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A review of bacteriological profile of acute pyogenic meningitis in a tertiary care center in Southwest Nigeria

Güneybatı Nijerya'da bir üçüncü basamak merkezde akut piyojenik menenjitin bakteriyolojik profilinin gözden geçirilmesi

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Ethics Committee Approval: Approval to use patient's laboratory report was sought and received from the Ethical Review Committee of the teaching hospital and an informed consent was received from the parent and caregiver of the participants.
Etik Kurul Onayı: Hastanın laboratuvar raporunu kullanma onayı arandı ve eğitim hastanesinin Etik İnceleme Kurulundan alındı ve katılımcıların ebeveyni ve bakıcısından bilgilendirilmiş bir onay alındı.

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Abstract

Aim: Pyogenic meningitis remain a major cause of mortality and morbidity in lower middle income countries. There exists a wide variability in antibiogram profile of infective causes of acute pyogenic meningitis seeking for individualized management protocol. This study aim to review a five years profile of isolates from suspected cases and evaluate the antibiogram of the infective agent in a tertiary hospital in South west Nigeria.

Methods: All patients presenting to the hospital with signs and symptoms suggestive of meningitis were evaluated. Aside random plasma glucose, CSF samples were sent for biochemistry, gene expert for tuberculosis and cultured on Blood agar, Chocolate agar and MacConkey agar for neonates and read after 24hours incubation.

Results: 393 of the 657,890 patients seen in the hospital over a five year period suspected to have meningitis were investigated, 22 (7%) had a positive culture. Streptococcus pneumoniae (31.8%), Haemophilus influenza (27.4%), other Enterobacteriaceae (18.2%), Pseudomonas aeruginosa (9.1%), Staphylococcus aureus (4.5%), Proteus mirabilis (4.5%) and Candida albicans (4.5%) were isolated.

Conclusion: Spectrum of causative bacterial agent is not different from documented in other parts of the country. Streptococcus pneumoniae predominance was reported which is sensitive to Ampicillin, Ceftriaxone, Cefotaxime and Penicillin. Empirical treatment with Ceftriaxone or Cefotaxime can be instituted while awaiting laboratory confirmation in suspected cases.

Keywords: Acute pyogenic meningitis, Lower middle income countries, Antibiogram, Southwest Nigeria

Öz

Amaç: Piyojenik menenjit, düşük orta gelirli ülkelerde önemli bir mortalite ve morbidite nedenidir. Bireyselleştirilmiş yönetim protokolü arayan akut piyojenik menenjitin enfektif nedenlerinin antibiyogram profilinde geniş bir değişkenlik vardır. Bu çalışmada, şüpheli vakalardaki izolatların beş yıllık bir profili gözden geçirilerek Güney Batı Nijerya'daki bir üçüncü basamak hastanede enfektif ajanın antibiyogramının değerlendirilmesi amaçlanmıştır.

Yöntem: Menenjit düşündüren belirti ve bulguları olan hastaneye başvuran tüm hastalar değerlendirildi. Rastgele plazma glukozunun yanı sıra, CSF örnekleri biyokimya, tüberküloz için gen uzmanı olarak gönderildi ve yenidoğanlar için Blood agar, Chocolate agar ve MacConkey agar üzerinde kültürlendi ve 24 saat inkübasyondan sonra okundu.

Bulgular: Hastanede menenjit geçirdiğinden şüphelenilen beş yıllık bir süre içinde görülen 657.890 hastanın 393'ü araştırıldı, 22'sinde (%7) pozitif kültür vardı. Streptococcus pneumoniae (%31,8), Haemophilus influenza (%27,4), diğer Enterobacteriaceae (%18,2), Pseudomonas aeruginosa (%9,1), Staphylococcus aureus (%4,5), Proteus mirabilis (%4,5) ve Candida albicans (%4,5) .

Sonuç: Nedensel bakteri ajanının spektrumu, ülkenin diğer bölgelerinde belgelenenlerden farklı değildir. Ampisilin, Ceftriaxone, Cefotaxime ve Penicillin'e duyarlı Streptococcus pneumoniae baskınlığı bildirilmiştir. Şüpheli vakalarda laboratuvar onayı beklenirken Ceftriaxone veya Cefotaxime ile ampirik tedavi uygulanabilir.

Anahtar kelimeler: Akut piyojenik menenjit, Düşük orta gelirli ülkeler, Antibiyogram, Güneybatı Nijerya

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Introduction

Cerebrospinal Meningitis (CSM), inflammation of the meninges, is a medical emergency affecting all age groups. It is a common cause of mortality and morbidity in all age groups especially children and presents with fever, headache, meningismus, and altered mental status. Pyogenic bacterial meningitis remains a major cause of mortality and morbidity in lower middle income countries. It can be of infectious or non-infectious origin. Etiologic agents in infectious CSM vary with age and presence of underlying morbidity such as head trauma, recent neurosurgery, presence of a cerebrospinal fluid (CSF) shunt and immunocompromised state. The onset and extent of symptom is dependent on the clinical type; acute meningitis presents within hours to few days while subacute and chronic meningitis has a more gradual and insidious onset. The causative agent also varies depending on the clinical type [1]. The common etiologic agents of acute meningitis are viruses commonly the enteroviruses, but also HIV, mumps virus, and herpes simplex viruses and bacteria such as Streptococcus pneumoniae, Neisseria meningitidis, and Listeria monocytogenes. Less commonly, protozoa such as Naegleria fowleri and Angiostrongylus cantonensis may cause acute meningitis. Mycobacteria especially Mycobacterium tuberculosis, spirochetes such as Treponema pallidum and Borrelia burgdorferi, and fungi such as Cryptococcus neoformans and Coccidioides spp. are implicated in subacute and chronic meningitis and it is commonly associated with immunosuppression. Previous studies has shown the predominant etiologic agent for pyogenic meningitis in 90% of cases were N. meningitides, S. pneumonia and H. influenza type b. Meningitis due to Neisseria meningitidis has epidemic potential, causing the syndrome of epidemic cerebrospinal fever which was first described in Geneva by Vieusseaux in 1805 [2]. Subsequent reports throughout the 19th century confirmed its episodic, epidemic nature with a propensity for afflicting young children and military recruits assembled in stationary barracks situations.2 Epidemic CSM in Nigeria is seen in conditions of overcrowding [3].

Diagnosis of CSM is confirmed in the laboratory by the presence of CSF White blood cell count of 1000-5000/mm3 (range 100 to 10,000) 80% or more of which are neutrophils, raised CSF Protein value 100-500mg/dL raised CSF glucose of 40mg/dL, CSF-to-serum glucose ratio 0.4, Gram stain Positive in 60%-90% and Culture Positive in 70%-85%. The probability of isolating and identifying the etiologic agent is less than 50% where antibiotics have been instituted before presenting to the hospital or before sample collection. Within 24 to 36 hours of administration of appropriate antimicrobial agent, initially positive CSF cultures became sterile in 90% to 100% of patients especially infants and children [4].

The mortality rate of untreated bacterial meningitis approaches a 100%. Even with optimal therapy, morbidity and mortality may occur [5]. In infants and children, signs and symptoms of meningitis do not allow distinguishing the diagnosis and the causative agents though it has been documented that it is predominantly aseptic in this age group and bacterial origin in very few cases (10-20%) [6]. The presentation irrespective of the causative agent is the same but neurologic sequelae is more frequent following bacterial meningitis especially when treatment is not instituted early enough and or the antibiotics used is ineffective. Laboratory evaluation of CSF in suspected cases takes minimum of 48 hours to confirm diagnosis; this time is essential in the effective treatment and recovery of individuals with meningitis hence institution of empirical therapy before retrieving laboratory confirmatory result has been advocated. In many cases of bacterial CSM, the causative agent isn't recovered from clinical specimen hence specific antimicrobial susceptibility testing cannot be carried out and diagnosis relies on positive gram stain, suggestive CSF biochemical reports and clinical presentation while choice of antibiotics to treat with is the sole prerogative of the managing physician [6,7]. The pattern and spectrum of bacterial meningitis causative agent in this environment need be investigated, their antibiotic susceptibility profile known in order to influence the choice of antibiotic used in empirical therapy before a definitive treatment is instituted. With this background knowledge, a change in trend or deviation from the norm for this geographical location can easily be noted. It is also known that there exists a wide variability in antibiogram profile of infective causes of acute pyogenic meningitis seeking for individualized management protocol.

As at April 3, 2017, a total of 2,997 suspected cases of CSM have been reported in 16 States in Nigeria and the FCT. Affected states are, according to The Ministry of Health, Lagos, Osun, Zamfara, Kano, Katsina, Sokoto, Kebbi, Niger, Nasarawa, Jigawa, FCT, Gombe, Taraba, Yobe, Cross Rivers, Oyo, Plateau [8-10]. This study is a clinical and laboratory evaluation of isolates from 2,345 patients with suspected bacterial meningitis over a period of 5 years at Bowen University Teaching Hospital, Ogbomoso in Oyo state which is one of the states where CSM has been reported in Nigeria and also a referral Centre for the 33 local government area in the state and neighboring states. It equally evaluates the antibiogram of the infective agent in the tertiary hospital in South west Nigeria.

Materials and methods

All patients seen in different arms of the hospital from January 2013 to January 2018 with suspected meningitis were evaluated clinically. Clinical case definition was patient presenting with fever, headache, meningismus, and altered mental status for older children and adults while poor feeding or sucking, convulsion, vomiting and loss of consciousness were considered in infants and children less than 2 years of age. Appropriate laboratory investigations were individualized. Lumber puncture was carried out on all suspected cases of meningitis under aseptic technique. Specimens were evaluated macroscopically and microscopically.

Laboratory confirmation of diagnosis was organism seen on Gram staining of the CSF with or without a positive culture of the CSF, elevated CSF protein and reduced CSF glucose less than one-half of blood glucose.

Aside random plasma glucose, samples were sent for biochemistry and gene expert for Mycobacterium tuberculosis. Total white cell count (WBC) above 6 cells/ mm3 was designated significant for patient age above 28 days while a

WBC of 30cells/ mm3 was significant for neonates. Samples were cultured on Blood agar, Chocolate agar, and MacConkey agar for neonates and incubated overnight. Culture plates were kept for minimum of 48 hours before being labelled as culture negative. Gram staining was done on all isolates, catalase and coagulase tests for the gram positive isolates and indole, motility; citrate utilization test was carried out on the gram negative isolates.

Statistical analysis

Data entry and management were done with Microsoft Excel. All analyses and calculations were performed using SPSS software (Statistical Package for Social Sciences). Relationship between categorical variables was done using Chi square or Fisher's exact test and for continuous variables using Student's t-test and $P<0.05$ was taken as significant value.

Results

Of the 657,890 seen in the hospital over the five year period, 393 were suspected to have meningitis. Bacterial agent was isolated in 22(7%) (Figure 1). Implicated organisms were Streptococcus pneumoniae (31.8%), Hemophilus influenza (27.4%), other Enterobacteriaceae (18.2%), Pseudomonas aeruginosa (9.1%), Staphylococcus aureus (4.5%), Proteus mirabilis (4.5%) and Candida albicans (4.5%) (Table 1). Irrespective of the age and sex of the patient, the causative agents were not isolated in most of the cases (Table 2). In children aged less than 2 years, Hemophilus influenza as a causative agent of meningitis predominated (table 3), while Streptococcus pneumoniae was the predominant agent in the older child aged above 2 years and adults. Pseudomonas aeruginosa was the only isolate recovered in young adults aged 12 years to 18 years (Table 3). Isolates were variably sensitive to antibiotics tested; all isolated strains of Streptococcus pneumoniae was resistant to Augmentin, Ceftazidime, Chloramphenicol, Clindamycin, Erythromycin, and the Fluoroquinolones tested against it. Hemophilus influenza strains were likewise resistant to chloramphenicol, ceftazidime, cefuroxime, cotrimoxazole, ceftriaxone, cefotaxime, erythromycin, levofloxacin and penicillin. The other enterobacteriaceae isolates were also multiply resistant, resistance to chloramphenicol, ceftazidime, ceftriazone, cefotaxime, pefloxacin, cotrimoxazole and erythromycin were reported. Pseudomonas aeruginosa strains were resistant to chloramphenicol, ceftazidime, ceftriazone, cefotaxime, erythromycin, levofloxacin, pefloxacin, penicillin, cotrimoxazole. Staphylococcus aureus isolate was sensitive to all antibiotics tested except penicillin while Proteus mirabilis was sensitive to all except clindamycin, cotrimoxazole and tetracycline (Table 4).

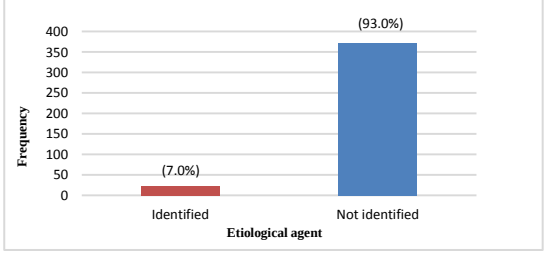

Figure 1: Frequency of isolation of etiologic agent

Table 1: Identified bacteria etiological agents of meningitis

Etiological agent	Frequency (n=22) n (%)
Streptoccocus pneumoniae	7 (31.8)
Haemophilus influenza	6 (27.4)
Other enterobacteriaceae	4 (18.2)
Pseudomonas aeruginosa	2 (9.1)
Staphyloccocus aureus	1 (4.5)
Proteus mirabilis	1 (4.5)
Candida albicans	1 (4.5)

Table 2: Identification of etiologic agent based on age and sex

Variable	Etiological agent Identified n (%)	Not identified n (%)	Total N (100.0%)	χ^2	*P*-value
Age					
0 – 1 month	2 (8.7)	21 (91.3)	23	0.432[Y]	0.994
>1 – 24 months	10 (8.4)	109 (91.6)	119		
> 24 – 60 months	3 (4.8)	59 (95.2)	62		
> 5 – 12 years	3 (8.3)	33 (91.7)	36		
> 12 – 18 years	1 (5.3)	18 (94.7)	19		
> 18 years	3 (5.4)	53 (94.6)	56		
Sex					
Male	9 (5.4)	158 (94.6)	167	1.392	0.238
Female	13 (8.8)	135 (91.2)	148		

χ^2: Chi square; Y: Yates Corrected Chi square

Table 3: Specific agents by age

Organism	Age group 0–1 month n (%)	1–24 months n (%)	>24–60 months n (%)	>5–12 years n (%)	>12–18 years n (%)	>18 years n (%)	Total n (%)
Streptococcus pneumoniae	1 (50.0)	2 (20.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (66.7)	7 (31.8)
Haemophilus influenza	0 (0.0)	5 (50.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (27.3)
Staphylococcus aureus	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Pseudomonas aeruginosa	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	2 (9.1)
Proteus mirabilis	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Candida albicans	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (4.5)
Other Enterobacteriaceae	1 (50.0)	1 (10.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)

Table 4: Antibiotic susceptibility profile of isolates

Antibiotics	Streptococcus (n = 7) S n (%)	R n (%)	Hemophilus (n = 6) S n (%)	R n (%)	Enteriobacteriacea(n=4) S n (%)	R n (%)	Pseudomonas(n=2) S n (%)	R n (%)	Staphyloccocus(n=1) S n (%)	R n (%)	Proteus(n=1) S n (%)	R n (%)
Ampicillin (AMP)	4 (57.1)	3 (42.9)	1 (16.7)	5 (83.3)	3 (75.0)	1 (25.0)	0 (0.0)	2 (100.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Augmentin(AUG)	0 (0.0)	7 (100.0)	3 (50.0)	3 (50.0)	1 (25.0)	3 (75.0)	0 (0.0)	0 (0.0)	O(0)	1(100)	1(100.0)	0 (0.0)
Ceftazidine(CAZ)	0 (0.0)	7 (100.0)	2 (33.3)	4 (66.7)	0 (0.0)	4 (100.0)	0 (0.0)	2 (100.0)	1(100)	O(0)	0 (0.0)	1(100.0)
Chloraphenicol (C)	1 (14.3)	5 (71.4)	0 (0.0)	6 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)	2 (100.0)	1(100)	O(0)	0 (0.0)	1(100.0)
Ciprofloxacin (CIP)	1 (14.3)	6 (85.7)	5 (83.3)	1 (16.7)	4(100.0)	0 (0.0)	2 (100.0)	0 (0.0)	O(0)	O(0)	1(100.0)	0 (0.0)
Cefuroxime (CFX)	0 (0.0)	5 (71.4)	0 (0.0)	6 (100.0)	2 (50.0)	2 (50.0)	0 (0.0)	2 (100.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Clindamicin(CL)	0 (0.0)	7 (100.0)	2 (33.3)	4 (66.7)	2 (50.0)	2 (50.0)	1 (50.0)	1 (50.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Cotrimoxazole (COT)	1 (14.3)	5 (71.4)	0 (0.0)	6 (100.0)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Ceftriaxone (CRO)	4 (57.1)	3 (42.9)	0 (0.0)	6 (100.0)	4 (100.0)	O(0)	2 (100.0)	0 (0.0)	1(100)	O(0)	1(100)	0 (0.0)
Cefotaxime (CTX)	2 (28.6)	4 (57.1)	0 (0.0)	6 (100.0)	4 (100.0)	O(0)	0 (0.0)	2 (100.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Erythromycin (ERY)	0 (0.0)	6 (85.7)	0 (0.0)	6 (100.0)	0 (0.0)	4 (100.0)	0 (0.0)	2 (100.0)	1(100.0)	O(0)	0 (0.0)	1(100.0)
Gentamicin (GEN)	1 (14.3)	3 (42.9)	5 (83.3)	1 (16.7)	2 (50.0)	2 (50.0)	2 (100.0)	0 (0.0)	1(100.0)	O(0)	1(100.0)	0 (0.0)
Levofloxacin(LVX)	0 (0.0)	7 (100.0)	0 (0.0)	6 (100.0)	1 (25.0)	3 (75.0)	0 (0.0)	2 (100.0)	1(100.0)	O(0)	0 (0.0)	1(100.0)
Ofloxacin (OFL)	0 (0.0)	7 (100.0)	2 (33.3)	4 (66.7)	2 (50.0)	2 (50.0)	1 (50.0)	1 (50.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Penicillin (PEN)	2 (28.6)	2 (28.6)	0 (0.0)	6 (100.0)	1 (25.0)	3 (75.0)	0 (0.0)	2 (100.0)	O(0)	O(0)	0 (0.0)	1(100.0)
Perfloxacin(PEF)	1 (14.3)	5 (71.4)	1 (16.7)	5 (83.3)	4 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	1(100.0)	O(0)	0 (0.0)	1(100.0)
Tetracycline (TET)	3 (42.9)	2 (28.6)	4 (66.7)	1 (16.7)	1 (25.0)	3 (75.0)	0 (0.0)	2 (100.0)	1(100.0)	O(0)	0 (0.0)	1(100.0)

Discussion

Seven percent of the 393 cases reviewed were confirmed by laboratory evidence of recovery of an isolate, this is similar to the report from a study carried out at the department of Child Health of the Royal Hospital where the records of 395 children suspected to have meningitis revealed only 7% of them to be abnormal [11].

Similar to the finding in this study is 5.2% recovery rate reported in National Hospital amongst children with suspected to have meningitis, and 6.2% reported at Ibadan [12,13]. This rate however is higher than the experience from Shagamu (2.8%), Maiduguri (3.5%) and Ilesha (1.6%) [14-16].

The low rate of isolating causative organism in meningitis reported in this study may be due to availability and assess to over-the-counter antibiotics and its commencement before sending samples to the laboratory, inappropriate use of antibiotics before presentation at the hospital, presence of nonculturable organisms as well as unfavorable culture conditions like erratic power supply, culture media not optimal hence can't support organism growth, transport conditions resulting in loss of viability of organism before it gets to the laboratory. Lack of microbiology resources for bacterial culture, and variable quality of microbiology services are among the reasons for culture negativity as stated by Ashraf et al. [5] Aseptic meningitis syndrome, a term used to define meningitis with a lymphocytic pleocytosis, for which a cause is not apparent

after initial evaluation and routine stains and cultures of CSF can also be the cause.

Isolates recovered were Streptococcus pneumonia, Hemophilus influenza, Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis, and other members of the family enterobacteriaceae and Candida albicans. The commonest pathogen isolated was Streptococcus pneumoniae (31.8%). Streptococcus pneumoniae predominance is similar to the finding in southern Nigeria in the 70s where a 5 year review revealed N. meningitidis, S. pneumoniae, H. influenza and other organisms, including S. aureus and enterobacteriaceae as causes of bacterial meningitis. The tide however has changed in recent times as a 5 year review carried out in the 80s, 10 years after the previous review, at the same center in Benin, Nigeria showed that the same organisms were responsible for the 253 culture proven cases of bacterial meningitis, however, commonest isolate was N. meningitides (49.8%), replacing S. pneumoniae as the commonest bacterial cause of infectious meningitis [17].

In tandem with the finding of this report however is the result from a study carried out at the Royal care hospital in the UK in which the commonest pathogen was Group B Streptococcus (70%) [11]. In Ilorin also, Johnson found out that Streptococcus pneumoniae as a cause of bacterial meningitis predominated (78.6%) followed by Hemophilus influenza (7.1%), and Neisseria meningitides was the least recovered isolate (3.5%) [18]. Hemophilus influenza type b (Hib) was however the leading pathogen at University College Hospital (UCH) ibadan, found in 16 (55.1%) of the 29 cases of definite meningitis. Other isolates include Streptococcus pneumoniae (24.1%), Klebsiella spp (7.0%), Staphylococcus aureus (7.0%), Escherichia coli (3.4%) and Pseudomonas spp. (3.4%) [19]. The relative downregulation of meningitis due to N. meningitidis may be because of the presence of vaccination program against it and the success and widespread use of the vaccine in the susceptible age group.

Varying degrees of resistance to antibiotics was seen in this study, of particular note is the resistance to chloramphenicol seen in all organisms. This finding underscores the stoppage of chloramphenicol as a drug of first line treatment, empirical or therapeutic, of bacterial meningitis.

The recommended WHO treatment guideline for management of bacterial meningitis in non-epidemic situations is ceftriaxone once a day for 5–7 days, availability and affordability especially at peripheral centers is however a disadvantage [20]. In epidemic situations, the principle is a free, simple presumptive treatment, available at peripheral level and Oily chloramphenicol is recommended in countries when available, otherwise ceftriaxone.

According to the WHO document on Epidemic and Pandemic Alert and Response, in non-epidemic situations, laboratory identification of the bacteria in cerebrospinal fluid should be done to guide choice of antibiotic. However, in some countries within the African meningitis belt, laboratory investigation of suspected meningitis cases is often unavailable hence, treatment should be adapted to the most probable causative pathogen according to age of the patient. Since 1996, WHO has recommended the use of oily chloramphenicol (OC) for the presumptive treatment of meningococcal epidemics in peripheral health centers. OC is effective as a single dose (100 mg/kg), easy to use at district level (one intramuscular injection), has a low risk of misuse due to its limited indication. In epidemic situations however, the principle of presumptive treatment is instituted in which case, rapid identification of the pathogen(s) circulating is crucial for an effective response. Laboratory investigation of suspected meningitis cases should be standard practice at the beginning of the meningitis epidemic season. After identification of an isolate in 95% of cases of bacterial meningitis seen in health centers, systematic laboratory confirmation is no longer necessary, and treatment should be adapted to the most probable causative pathogen, which is that isolate [20].

The use of chloramphenicol however is supported by Sanya et al. [21] and Ozumba [22] following the favorable outcome reported at their centers when the drug was combined with crystalline penicillin. In the UCH Ibadan study, Hib and pneumococcus showed varying degrees of resistance to chloramphenicol, penicillin and cotrimoxazole as was reported in this review [19]. Hemophilus influenza, Neisseria meningitidis, Staphylococcus aureus and Escherichia coli were isolated in Ilesa, Osun state and all isolates were sensitive to both ceftriaxone and ciprofloxacin while the sensitivities to penicillin and ampicillin were remarkably low [23]. This is likely due to the availability and affordability of ampicillin hence its widespread abuse resulting in development of resistance.

Limitation of the study

Late presentation of cases to the hospital, after use of oral and parenteral antibiotics procured over the counter. Adult patients and caregivers of pediatric patients are not willing to concede to lumbar puncture to collect sample.

Conclusion

Spectrum of causative bacterial agent is not different from documented in other parts of the country. There is Streptococcus pneumoniae predominance which is sensitive to Ampicillin, Ceftriaxone, Cefotaxime and Penicillin. Hence in confirmed cases or suspected cases, empirical treatment with Ceftriaxone or Cefotaxime can be instituted while awaiting laboratory confirmation.

Recommendation

Frequent review of the causes of pyogenic meningitis and their antibiotic sensitivity pattern is desirable to identify changes and/or trends if any. A local guideline need be drawn to help in the diagnosis and treatment of bacterial meningitis in view of the changing susceptibility of isolates to common antimicrobial agents.

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Impact of serum adipokines on tumor mitotic and apoptotic activity in endometrial cancer

Endometrial kanserde serum adipokinlerin tümör mitotik ve apoptotik aktiviteye etkisi

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Abstract

Aim: Endometrial cancer is the most common malignancy of female genital system. Obesity is one of the most important risk factors in endometrial cancer. Adipose tissue functions just like an endocrine organ by secreting many bioactive substances and contribute to tumor development. The aim of this study was to investigate the correlation between serum adipokine levels and tumor mitotic and apoptotic activity levels in endometrial cancer.

Methods: We designed a cross-sectional study. After obtaining the approval of Ethics Committee, 38 patients with endometrial cancer admitted between 2014 July-2014 December to Obstetrics and Gynecology outpatient clinic of Ondokuz Mayıs University, Faculty of Medicine were included in the study. Serum leptin and adiponectin levels were measured in 5 cc serum samples taken from the patients preoperatively. The pathology specimens of the patients were semi quantitatively evaluated with immunohistochemical study considering the percentage and intensity of staining for bcl-2 and the percentage of staining for Ki67. Moreover, preoperative estradiol levels, insulin resistance, body fat percentages and body mass index (BMI) values were determined. The Mann Whitney U test, Kruskal Wallis and Spearman's Correlation test were used statistically. The results were considered statistically significant for $P<0.05$.

Results: The patients included in the study were between 36-82 years of age and the mean age was 62.5 (10.4) years. The mean BMI value of the patients was 31.1 (4.8) kg/m2 (range: 19-38 kg/m^2). According to the FIGO 2010 staging system, the distribution of the patients were as follows: 30 patients (78%) Stage 1, 1 patient (2.6%) Stage 2 and 7 patients (18.4%) Stage 3. Of the patients, 6 (15.8%) had grade 1, 20 (52.6%) had grade 2 and 12 (31.6%) had grade 3. Twenty-seven patients were classified as endometrioid type and 11 patients were classified as nonendometrioid type. There was no statistically significant correlation between serum leptin and adiponectin levels and percentage of Ki-67 immunohistochemical staining in tumoral tissue and bcl-2 score ($P=0.05$). In the immunohistochemical examination of tumoral tissue, it was found that tumor grade statistically significantly increased as the staining percentage for Ki67 increased (r=0.571, $P<0.001$). There was no statistically significant correlation between Bcl-2 score and tumor grade or stage ($P=0.751$). It was found that serum leptin levels significantly increased as BMI increased (r=0.341, $P=0.036$). As HOMA-IR increased, adiponectin level statistically significantly increased (r=0.393, $P=0.015$). There was also no statistically significant difference between the endometrioid and non-endometrioid groups in terms of leptin, adiponectin and leptin/adiponectin levels ($P=0.554$, $P=0.652$). There was no statistically significant difference between the endometrioid and non-endometrioid groups in terms of median BCL-2 score and Ki-67 percentage ($P=0.05$).

Conclusion: There was no correlation between serum leptin and adiponectin levels and Ki-67 immunohistochemical staining percentage and bcl-2 score.

Keywords: Endometrial cancer, Adipokines, Apoptosis, Immunohistochemistry

Öz

Amaç: Endometrial kanser, kadın genital sisteminin en sık görülen malignitesidir. Obezite, endometrial kanserde en önemli risk faktörlerinden biridir. Adipoz doku, birçok biyoaktif madde salgılayarak tıpkı bir endokrin organı gibi işlev görür ve tümör gelişimine katkıda bulunur. Endometrium kanserinde serum adipokin seviyeleri ile tümör mitotik ve apopitotik aktivite düzeyleri arasındaki ilişkinin araştırılması amaçlanmıştır.

Yöntemler: Kesitsel bir çalışma tasarladık. Etik Kurul onayı alındıktan sonra 2014 Temmuz-2014 Aralık tarihleri arasında Ondokuz Mayıs Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum polikliniğine endometriyal kanserli 38 hasta dahil edildi. Hastalardan preoperatif alınan 5 cc serum örneğinde serum leptin ve adiponektin seviyesi ölçüldü. Hastaların patoloji spesmenleri immünhistokimyasal çalışma ile bcl-2 için boyanma yüzdesi ve şiddeti ve Ki67 için boyanma yüzdesi gözönüne alınarak semikantitatif olarak değerlendirildi. Ayrıca hastaların preoperatif östradiol seviyesi, insülin direnci, vücut yağ oranları ve body mass index (BMI) değerleri belirlendi. İstatistiksel olarak Mann Whitney U Kruskal Wallis ve Spearman'ın Korelasyon testi kullanıldı. $P<0,05$ için sonuçlar istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya alınan hastalar 36-82 yaşlar arasında olup yaş ortalaması 62,5 (10,4) idi. Hastaların ortalama BMI değeri 31,1 (4,8) kg/m^2 idi (Aralık: 19-38 kg/m^2). FIGO 2010 evreleme sistemine göre 30 hasta (%78) Evre 1, 1 hasta (%2,6) Evre 2,7 hasta (%18,4) Evre 3 olarak dağılım göstermekte idi. Hastaların 6 tanesi (%15,8) grade 1, 20 tanesi (%52,6) grade 2 ve 12 tanesi (%31,6) grade 3 olarak dağılım göstermekte idi. 27 hasta endometrioid tip kalan 11 hasta nonendometrioid tip olarak sınıflandırıldı. Serum leptin ve adiponektin düzeyi ile tümöral dokuda Ki-67 immünhistokimyasal boyanma yüzdesi ve bcl-2 skoru arasında istatistiksel anlamlı korelasyon saptanmadı ($P=0,751$). Tümöral doku immünhistokimyasal incelemesinde Ki67 için boyanma yüzdesi arttıkça tümörün grade'i de istatistiksel anlamlı olarak arttığı belirlendi (r=0,571 $P<0,001$). Bcl-2 skoru ile tümör grade veya evresi arasında istatistiksel anlamlı korelasyon saptanmadı ($p>0.05$). BMI arttıkça serum leptin düzeylerinin istatistiksel anlamlı olarak arttığı saptandı (r=0,341, $P=0,036$). HOMA-IR arttıkça adiponektin düzeyi istatistiksel anlamlı olarak artmaktaydı (r=0,393, $P=0,015$). Endometrioid ve non-endometrioid gruplar arasında da; leptin, adiponektin ve leptin/adiponektin düzeyleri yönünden istatistiksel olarak anlamlı farklılık görülmedi ($P=0,554$, $P=0,652$). Endometrioid ve non-endometrioid grupları arasında medyan BCL-2 skoru ve Ki-67 yüzdesi yönünden istatistiksel olarak anlamlı farklılık görülmedi ($P=0,05$).

Sonuç: Serum leptin ve adiponektin düzeyi ile tümöral dokuda Ki-67 immünhistokimyasal boyanma yüzdesi ve bcl-2 skoru arasında istatistiksel anlamlı korelasyon yoktur.

Anahtar kelimeler: Endometrium kanseri, Adipokin, Apopitozis, İmmunohistokimya

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Introduction

Endometrial cancer is the most common malignancy of female genital system. Obesity is one of the most important risk factors in endometrial cancer. Therefore, the effect of numerous bioactive substances released from adipose tissue on tumor development has been investigated. Adiponectin and leptin are the most important adipokines released from adipose tissue. Today, serum L/A (leptin/adiponectin) ratio has been shown to increase in many cancers associated with obesity [1,2].

Leptin is the product of the Ob gene expressed by adipocytes in adipose tissue; it is similar to cytokines and is a protein hormone containing 167 amino acids. It is encoded by the ob/ob gene residing on the long arm of chromosome 7 (7q31). It has also been shown to be secreted by some placenta, gastric epithelium, skeletal muscle, pituitary and mammary gland. It circulates in free and protein-bound form in the blood. The free form is thought to be responsible for leptin activity. The level of serum leptin increases in proportion to the amount of adipose tissue in the body. It is higher in women than in men. After being released into the blood circulation, it binds to its receptors in the hypothalamus and prevents the development of obesity by establishing a balance between the body's energy requirement and weight gain with a negative feedback effect. About 6 different receptors of leptin have been identified in various tissues. It has also been found to play very important roles in metabolic regulation, sexual development, reproduction, hematopoiesis, immunity, regulation of gastrointestinal functions, sympathetic nervous system activation, angiogenesis and osteogenesis [3,4]. In the early secretory phase, expression of leptin receptors increases in the endometrium. Progesterone reduces the level of leptin receptor in the endometrium [5].

Leptin has been shown to play a role in the proliferative processes in breast, endometrium, prostate, colon and many other tissues [1,2].

Adiponectin is a protein molecule with a weight of 30 kDa. Adiponectin is negatively correlated with obesity. Low adiponectin levels are associated with hyperinsulinemia and increased insulin resistance [6]. Two different adiponectin receptors have been identified in the tissue.

The L/A ratio is an indicator of insulin resistance in diabetic and nondiabetic patients [7,8]. Serum L/A ratio has been found to be high in breast, colon and endometrial cancer, and is more significant than increased leptin level alone [9,10]. In addition, high L/A ratios in endometrial cancer are associated with increased risk independent of diabetes and obesity. The presence of independent risk increase is explained by the fact that these adipokines contribute directly to the pathophysiologic mechanisms in tumor formation.

High leptin levels cause increased insulin resistance and hyperinsulinemia [11,12]. Moreover, leptin increases estrone formation from androstenedione by increasing the aromatase activity in peripheral adipose tissue [1]. In addition, by increasing (estrogen receptor) ER alfa stability, it increases the formation of estrogenic effects in the tissue. Adiponectin deficiency causes insulin resistance. It has been shown that serum adipokines also cause an increased risk in endometrial cancer independent of estrogen and insulin [13]. It has been shown that leptin increases the proliferation and invasiveness of tumor cells using the JAK/STAT and ACT pathways, while adiponectin decreases tumor proliferation by causing apoptosis [14,15].

Our study aims to investigate the effects of adipokines on tumor proliferation by comparing serum leptin and adiponectin levels with bcl-2 (anti-apoptotic protooncogen) and Ki67 (proliferation markers) levels in the tumoral tissue of patients with endometrial cancer. In addition, the correlation between serum estrogen level, body mass index (BMI), body fat percentage and insulin resistance (HOMA-IR) and serum leptin and adiponectin levels in endometrial cancer will be evaluated.

Materials and methods

Ethical committee approval was obtained (OMU-KAEK-2014/768-788). The informed consent was obtained from all participants.

Patient selection

The study included 38 patients admitted to the Obstetrics and Gynecology Outpatient Clinic of Ondokuz Mayıs University and diagnosed with endometrial cancer and scheduled for operation. We included all endometrial cancer patients between 2014 July-2014 December in this study. It is a cross-sectional study. While selecting the patients, the diagnosis of endometrial cancer was made by endometrial biopsy. Patients who were not scheduled for surgery because of systemic diseases or who refused surgery despite recommendation for surgery were excluded from the study.

Collection and storage of serums

Before the operation, serum samples of about 5-6 cc were taken from the antecubital region in the sitting position at room temperature (24 C) using the standard blood collection technique after the sterilization of the area with a alcohol infused cotton. The blood samples taken were transferred in vacuum biochemistry tubes with red cap that did not contain any anticoagulant agent. The tubes were centrifuged at 5000 rpm for 5 minutes and stored at -80 ° C until the time of supernatant study.

Study of serum leptin and adiponectin levels

The serum samples stored at -20°C were thawed at room temperature, and then studied using the leptin ELISA Kit (DRG, Germany) and adiponectin ELISA Kit (Assaypro, USA) microelisa kit in accordance with the manufacturer's recommendations in the Elisa research laboratory. During the study, a microplate washer (BIO-TEK, ELX-50 model, USA) was used, and for the results, a microplate reader (BIO-TEK ELX800 model, USA) was used. All parameters were read at a wavelength of 450 nanometers and the absorbance values were placed in their area in the calibration graph to obtain the results of the samples. The Human Leptin Elisa Kit Assay range was given as 1.25-80 ng/ml, the Human Adiponectin Elisa Kit Assay range as 0.7 ng/ml, and the intraassay and interassay as 4.3% and 7.2%. The results were interpreted.

Immunohistochemical staining and evaluation of the pathology specimens

All tissues of the patients that were sent to the pathology department after surgery were fixated in 10% neutral formalin solution and were blocked in paraffin. One block without

bleeding or necrosis representing the best histomorphology was selected from each case. Sections of 5 microns were taken from the selected blocks using microtome devices. Using immunohistochemical staining devices (Ventana, Benchmark, XT, USA) on the sections, immunohistochemical study was carried out with Ki67 (Anti Ki-67, Fremant CA 94538, Emego Europe, Netherlands) and bcl-2 (Bcl-2 oncoprotein, NCL-L-bcl-2, Newcastle Upon tyne NE128EW, United Kingdom) primary antibodies.

The staining results were semi quantitatively evaluated by a pathologist under a Olympus Bx51 under light microscope (Olympus, USA, 1999) considering the percentage and intensity of staining for bcl-2 and the percentage of staining for Ki67 (Table 1, 2) (Figure 1, 2, 3).

Table 1: Immunohistochemical evaluation of Bcl-2

Parameter	Score
A - Staining intensity	(0 – 3)
Negative	0
Weak staining	1
Moderate staining	2
Strong staining	3
B - Staining percentage (percentage of stained cells)	(0 – 4)
No staining of tumor cells or staining in less than 5% of tumor cells	0
Staining in 5-25% of tumor cells	1
Staining in 25-50% of tumor cells	2
Staining in 50-75% of tumor cells	3
Staining in more than 75% of tumor cells	4
Total score (A + B)	(0 – 7)
Negative	0-1
Weak positive	2-3
Moderate positive	4-5
Strong positive	6-7

Table 2: Immunohistochemical evaluation of Ki67

	Staining percentage (percentage of stained cells)
0	0-10%
1	10-50%
2	50-75%
3	>75%

In the statistical evaluation, the data were evaluated according to the score for bcl-2 and the staining percentage for Ki67.

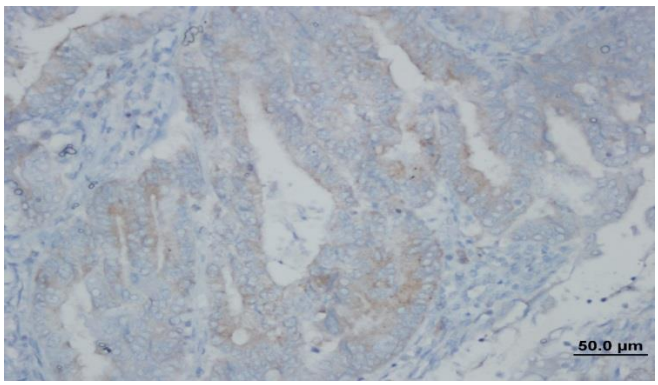

Figure 1: Endometrial cancer: Bcl-2, weak staining (DAB, X400)

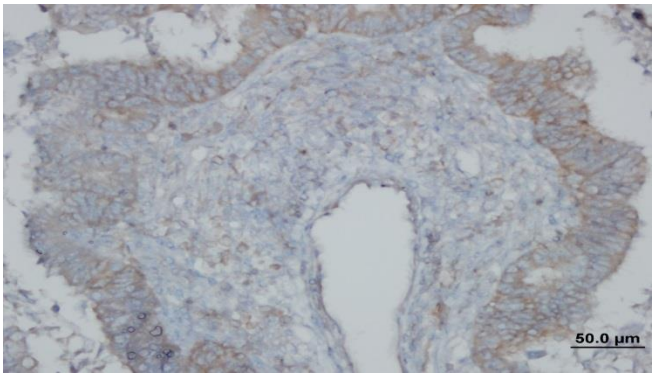

Figure 2: Endometrial cancer: Bcl-2; moderate staining (DAB, X400)

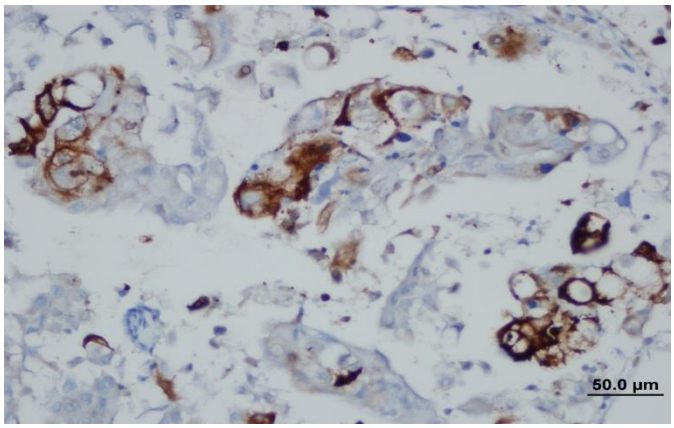

Figure 3: Endometrial cancer: Bcl-2; strong staining (DAB, X400)

Calculation of insulin resistance and preoperative estradiol level

Fasting glucose, insulin levels and estradiol levels were studied in 5 cc serum samples taken preoperatively after 8 hours of fasting.

The patients' insulin resistance was calculated using HOMA-IR (The Homeostatic Model Assessment of Insulin Resistance).

HOMA-IR: Fasting blood glucose (mg/dl).Fasting insulin microU/ml/405 (process constant value)

Calculation of body mass index and determination of body muscle-fat percentage of the patients

By measuring the heights and weights of the patients, BMI was calculated using body weight (in kg)/height squared (square meter) formula.

The body fat percentages of the patients were measured using Tanita-TBF 310 Body composition analyzer.

Statistical analysis

The analysis of the data was made on SPSS 11.5 software package for Windows. The Shapiro–Wilk test was used to analyze whether the continuous numerical variables are normally distributed, while Levene's test was used to analyze the homogeneity of variances. The descriptive statistics, the continuous numerical variables were expressed as mean (standard deviation), the ordinal variables as median (minimum-maximum), and the categorical variables as case number and (%). The significance of difference between the groups in terms of median values was analyzed by the Mann Whitney U test when the number of independent groups was two, while the significance of difference between more than two groups was analyzed by the Kruskal Wallis test. The Spearman's correlation test was used to determine whether there was a statistically significant correlation between variable pairs. The results were considered statistically significant for $P<0.05$.

Results

Clinicopathological and demographic characteristics of the patients

The patients included in the study were between 36-82 years of age and the mean age was 62.5 (10.4) years. The mean BMI value of the patients was 31.1 (4.8) kg/m^2 (range: 19-38 kg/m^2).

According to the FIGO 2010 staging system, the distribution of the patients were as follows: 30 patients (78%) Stage 1, 1 patient (2.6%) Stage 2 and 7 patients (18.4%) Stage 3.

Of the patients, 6 (15.8%) had grade 1, 20 (52.6%) had grade 2 and 12 (31.6%) had grade 3.

27 patients were classified as endometrioid type and 11 patients were classified as nonendometrioid type (Table 3).

Table 3: Demographic and clinical characteristics of the patients

Variables	n=38
Age (years)	62.5(10.4)
Age range (years)	36-82
Body mass index (kg/m^2)	31.1(4.8)
Fat mass	33.7 (14.3-47.2)
Type	
Endometrioid	27 (71.1%)
Non-endometrioid	11 (28.9%)
Stage	
I	30 (78.9%)
II	1 (2.6%)
III	7 (18.4%)
Grade	
I	6 (15.8%)
II	20 (52.6%)
III	12 (31.6%)

The correlation between serum leptin and adiponectin levels and Ki67 immunohistochemical staining percentage and Bcl-2 score

There was no statistically significant correlation between serum leptin level and percentage of Ki-67 immunohistochemical staining in tumoral tissue and bcl-2 score (P=0.554).

There was no statistically significant correlation between serum adiponectin level and percentage of Ki-67 immunohistochemical staining in tumoral tissue and bcl-2 score (P=0.652) (Table 4).

Table 4: Laboratory measurements of the patients

Variables	Mean	SD	Median	Minimum	Maximum
HOMA-IR	6.2	9.80	3.2	0.4	46.0
Leptin	6.5	5.59	5.1	0.0	21.9
Adiponectin	7.8	6.38	4.3	0.9	23.6
Leptin/Adiponectin	1.4	1.76	0.8	0.0	7.8
Estrogen	21.2	19.33	17.0	5.0	113.0

SD: Standard deviation

Immunohistochemical evaluation results for Bcl-2 and Ki-67

When the patients were immunohistochemically evaluated in terms of staining percentage for Ki67, it was found that there were 9 patients (23.7%) showing 0-10 percent staining, 16 patients (42.1%) showing 10-50 percent staining, and 5 patients (8.2%) showing 50-75 percent staining, and 8 patients (21.1%) showing >75 percent staining.

When the patients were immunohistochemically evaluated in terms of staining percentage for bcl-2, it was found that there were 13 patients (34.2%) with negative staining, 11 patients (28.9%) with 5-25 percent staining, 3 patients (7.9%) with 25-50 percent staining, 5 patients (13.2%) with 50-75 percent staining, and 6 patients (15.8%) with >75 percent staining.

When the patients were immunohistochemically evaluated in terms of staining intensity for bcl-2, it was found that the staining intensity was negative in 12 patients (31.6%), weak in 13 patients (34.2%), moderate in 11 patients (28.9%), and strong in 2 patients (5.3%) (Table 5).

Correlation between percentage of Ki67 staining in tumoral tissue and bcl-2 score and tumor grade and stage

In the immunohistochemical examination of tumoral tissue, it was found that tumor grade statistically significantly increased as the staining percentage for Ki67 increased (r=0.571 P<0.001).

There was no statistically significant correlation between Bcl-2 score and tumor grade or stage (P=0.751 and P=0.622, respectively).

There was no statistically significant correlation between Bcl-2 score and BMI, HOMA-IR and estrogen level (P=0.275, P=0.135 and P=0.569, respectively).

There was no statistically significant correlation between percentage of Ki67 staining and BMI, HOMA-IR, FIGO stage and estrogen level (P=0.540, P=0.365, P=0.130 and P=0.855, respectively) (Table 6).

Table 5: Descriptive statistics for BCL-2 and Ki-67 staining status

Variables	n=38
BCL-2 Intensity	
Negative	12 (31.6%)
Weak	13 (34.2%)
Moderate	11 (28.9%)
Strong	2 (5.3%)
BCL-2 percentage	
Negative or <5%	13 (34.2%)
5-25%	11 (28.9%)
25-50%	3 (7.9%)
50-75%	5 (13.2%)
>75%	6 (15.8%)
BCL-2 Score	2.5 (0-6)
Ki-67 staining percentage	
0-10%	9 (23.7%)
10-50%	16 (42.1%)
50-75%	5 (13.2%)
>75%	8 (21.1%)

Table 6: Correlation coefficients and significance levels between BCL-2 score and Ki-67 percentage and other clinical and laboratory measurements

	BCL-2 Score		Ki-67	
	r	P-value †	r	P-value †
BMI	-0.182	0.275	0.103	0.540
Stage	0.083	0.622	0.250	0.130
Grade	-0.053	0.751	0.571	<0.001
HOMA-IR	0.247	0.135	0.151	0.365
Estrogen	0.095	0.569	-0.031	0.855

r: Correlation coefficient, † Spearman's correlation test

Determination of the correlation between serum adipokine levels and BMI, body fat percentage, serum estrogen level and insulin resistance (HOMA-IR):

There was no statistically significant correlation between serum adipokine levels and tumor grade and stage (P=0.225, P=0.915, P=0.304 and P=0.418, respectively).There was no statistically significant correlation between serum leptin levels and serum estrogen level, body fat percentage and HOMA-IR (P=0.784, P=0.059 and P=0.975, respectively). On the other hand, in our study group of patients with endometrial cancer, it was found that serum leptin levels statistically significantly increased as BMI increased (r=0.341, P=0.036).

There was no statistically significant correlation between serum adiponectin level and serum estrogen level, BMI, body fat percentage (P=0.115, P=0.125 and P=0.082, respectively). On the other hand, as HOMA-IR increased, adiponectin level statistically significantly increased (r=0.393, P=0.015) (Table 7).

Table 7: Correlation coefficients and significance levels between Leptin, Adiponectin and Leptin/Adiponectin levels and other demographic, clinical and laboratory measurements

	Leptin		Adiponectin		Leptin/Adiponectin	
	r	P-value †	r	P-value †	r	P-value †
Age	0.131	0.432	0.070	0.676	-0.039	0.814
BMI	0.341	0.036	0.087	0.603	0.254	0.125
Stage	0.202	0.225	-0.029	0.864	0.171	0.304
Grade	-0.018	0.915	-0.055	0.742	0.135	0.418
HOMA-IR	-0.005	0.975	-0.393	0.015	0.260	0.115
Fat mass	0.309	0.059	-0.010	0.951	0.286	0.082
Estrogen	0.046	0.784	-0.286	0.081	0.260	0.115

r: Correlation coefficient, † Spearman's correlation test

Comparison of the endometrioid and nonendometrioid groups

There was no statistically significant difference between the endometrioid and non-endometrioid groups in terms of leptin, adiponectin and leptin/adiponectin levels, respectively. There was no statistically significant difference between the endometrioid and non-endometrioid groups in terms of median BCL-2 score and Ki-67 percentage.

Discussion

Endometrial cancer is the most common malignancy of female genital system. Obesity is one of the most important risk factors in endometrial cancer. Adipose tissue functions just like an endocrine organ by secreting many bioactive substances, and contributes to tumor development. Leptin and adiponectin, called serum adipokines, are cytokines which are released from adipose tissue and contribution of which to tumor development has been frequently investigated. In the study by Yu Ma et al. [16] investigating 206 patients with endometrial cancer and 310 healthy controls, it was found that serum leptin levels were significantly increased in the endometrial cancer group than in the control group. It was found that adiponectin levels of the endometrial cancer patients were borderline statistically significantly lower than that of the control group. In the study by Friedenreich et al. [17] included 541 endometrial cancer patients and the control group of 961 individuals, the correlation between insulin resistance markers (leptin, adiponectin, A:L, HOMA-IR) and the risk of endometrial cancer was investigated, and it was found that as insulin and HOMA-IR increased, the risk of endometrial cancer increased, and as the level of adiponectin increased, the risk of endometrial cancer decreased. There was no correlation between fasting blood glucose, leptin and A:L ratio and endometrial cancer. In the study by Cymbaluk et al. [18] comparing 40 patients diagnosed with endometrial cancer and 46 patients diagnosed with endometrial hyperplasia and the control group of 46 individuals with normal endometrium, a positive correlation between serum leptin levels and BMI was found. The mean serum leptin concentration was significantly higher in the endometrial cancer and endometrial hyperplasia groups than in the control group. Three groups were formed by considering BMI, and it was found that leptin levels of patients with endometrial pathology were significantly higher in each BMI group than in the control group. In the study by Mihu et al. [19] enrolled 44 endometrial cancer patients and the control group of 44 healthy subjects, the amount of abdominal fat was measured using (dual X-ray absorptiometry) DXA, and it was demonstrated that the amount of abdominal fat increased directly proportional to leptin and inversely proportional to adiponectin. It was also found that abdominal fat and serum leptin levels were significantly higher and adiponectin levels were significantly lower in patients with endometrial cancer than in the control group. In the study by Ashizawa et al. [13] comparing 146 patients diagnosed with postmenopausal endometrial cancer and the control group of 150 individuals, it was found that serum leptin levels and L/A ratios were significantly higher in patients with endometrial cancer than in the control group. Adiponectin levels of patients with endometrial cancer were found to be significantly lower than that of the control group. In the endometrial cancer group, a significant correlation was found between serum adipokine levels and BMI. There was a significant correlation between leptin level and L/A ratio and HOMA-IR. In patients with endometrial cancer, depending on the levels of leptin or adiponectin alone, L/A ratio was found to be more significant in determining the risk of endometrial cancer, and it was stated that L/A ratio was significant in determining the risk of endometrial cancer independent of obesity, hypertension and diabetes. There was no statistically significant correlation between serum adipokines or L/A ratio and tumor grade or FIGO stage. In our study, serum leptin level statistically significantly increased as BMI increased in the patients with endometrial cancer. However, there was no statistically significant correlation between leptin and HOMA-IR, fat mass and preoperative estrogen levels, respectively. In accordance with the literature, there was no significant correlation between tumor stage and grade and leptin, adiponectin or L/A. There was no statistically significant correlation between adiponectin and BMI, fat mass and estrogen levels, respectively. On the other hand, unlike the literature, adiponectin level statistically significantly increased as HOMA-IR level increased. There was no statistically significant correlation between L/A ratio and BMI, body fat percentage, HOMA-IR and estrogen levels. The fact that the correlation between adipokine levels and endometrial cancer risk was found to be significant independent of obesity in the studies conducted suggested that adipokines may play a direct role in tumor proliferation independent of estrogen and insulin [13,16]. It has been shown that leptin increases the proliferation and invasiveness of tumor cells using the JAK/STAT and ACT pathways, while adiponectin decreases tumor proliferation by causing apoptosis [14,15]. In the study by Sharma et al. [20], it was shown that leptin increased the invasiveness and proliferation of tumor using JAK / STAT and ACT pathways in endometrial cancer cells. In numerous studies, bcl-2 has been evaluated as an anti-apoptotic oncoprotein and Ki67 as a proliferation marker for endometrial cancer. In the study by Henderson et al. [21] on endometrial tissues of proliferative, hyperplastic, atypical hyperplastic and endometrial cancer, it was found that bcl-2 expression (bcl-2 score, defined as 0-4) was higher in proliferative (n:11, score: 3.59) and hyperplastic (n:18, score: 3.47) endometrium than in atypical hyperplasia (n:11, score: 0.82) and adenocarcinoma (n:34, score: 0.86) ($p < 0.001$). Moreover, it was also shown that there was no statistically significant correlation between bcl-2 expression and stage and grade in endometrial cancer group. In the study by Vaskivuo et al. [22], grade 1 (n:16), grade 2 (n:6), grade 3 (n:6) endometrial cancer specimens were analyzed and it was found that BCL-2 staining intensity (0: negative, 1: limited, 2: moderate, 3: strong staining) decreased inversely proportional to grade ($P<0.05$). They found that BCL-2 expression was high in normal proliferative endometrium and decreased in line with the severity of aggression in endometrial hyperplasia and cancer. In the study by Zheng et al. [23] comparing 21 endometrioid and 21 uterine papillary serous carcinomas, it was shown that endometrioid endometrial cancers had a higher immunohistochemical staining for bcl-2 than that of uterine papillary serous carcinoma ($P=0.002$). In the study by Canlorbe et al. [24] on 69 patients

with the diagnosis of endometrial cancer, it was found that immunohistochemical staining for ki-67 was higher in patients with grade 3 endometrial cancer than in those with grade 1 and 2 (P<0.001). Pinheiro et al. [25] divided 515 patients undergone hysteroscopic polypectomy into two groups as obese and nonobese, examined the specimens and found no significant difference between obese and nonobese groups in terms of Ki67 expression. Whereas, they found that Bcl-2 expression was higher in obese patients than in nonobese patients. In the study by Villavicencio et al. [26], 31 patients with benign endometrial tissue were divided into three groups based on their body mass index and 10 patients with type1 endometrial cancer were enrolled as the control group. In their study, a positive correlation was found between Ki67 percentage in endometrial tissues and serum leptin, insulin, estrogen levels and BMI of patients with benign endometrial tissue (P<0.05). In our study, there was no statistically significant correlation between serum adipokines and Ki67 percentage in tumoral tissue and BCL-2 score, and there was also no significant correlation between L/A ratio and Ki67 percentage and BCL-2 score. In our study, Ki67 staining percentage of the tumor statistically significantly increased as tumor grade increased. There was no statistically significant correlation between tumor stage and Ki-67 and Bcl-2 scores. There was no statistically significant correlation between tumor grade and BCL-2 score. There was no statistically significant correlation between BMI, HOMA-IR and estrogen levels and Ki67 percentage or Bcl-2 score. There was no statistically significant difference between the endometrioid and non-endometrioid groups in terms of median BCL-2 score and Ki-67 percentage.

Yuan et al. [27] investigated 80 cases of cervical cancer and found a statistically significant correlation between tumoral tissue leptin levels and tumor grade and Ki67 expression, and a positive correlation between tissue leptin level and bcl-2 expression. This study demonstrates the correlation between tumoral tissue leptin levels and tumor proliferative markers. However, serum adipokine levels were not investigated in this study. Although many experimental studies have shown the cell proliferation-promoting and apoptosis suppressive effects of leptin in cancer cells) [20,28], and although a significant correlation has been found between local leptin levels and tumor Ki67 and bcl-2 levels in many tumors [27] the absence of a study comparing serum adipokines with tumoral tissue proliferation markers was indicated as the most important weakness in these studies [28]. Because the studies have shown that serum adipokine levels are not a reflection of tissue adipokine levels [29]. Although serum leptin level increased in direct proportion to BMI in the study by Jeong et al. [28], they showed that adipokine levels in tumoral tissue were not correlated with BMI, and argued that local adipocyte tissue in tumoral tissue secretes adipokine locally and its participation in peripheral circulation is low. The results of our study support this hypothesis.

After adipokines are released from adipose tissue, they exhibit endocrine (being effective in all peripheral organs by participating in circulation), autocrine (being effective in the cell it is secreted) and paracrine (causing local effect in adjacent tissue) effects. For example, while it regulates energy metabolism with its endocrine effects, its paracrine effect is involved in wound healing. Our results support these mechanisms of action. Regulation of body weight is an endocrine function of leptin, in other words, the level of free-circulating leptin in serum determines this, and in line with this, serum leptin level increased as BMI increased in our study. However, there was no correlation between tumor Ki67 and bcl-2 level and serum adipokine levels, since tumor development may be related to local leptin level with paracrine effect. The most important weakness of our study is that we could not study serum adipokine levels and tissue adipokine levels simultaneously. However, our study is quite important in terms of being the first study in the literature investigating the correlation between serum adipokines and tumor mitotic and apoptotic markers in endometrial cancer to the best of our knowledge. Further studies investigating the relevant serum and tissue adipokines simultaneously in a larger sample size are needed.

Conclusion

Our study found that Ki67 expression determined by immunohistochemical examinations in patients with the diagnosis of endometrial cancer increased as tumor grade increased; however, there was no correlation between Ki67 expression and serum adipokine levels.

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Comparison of fluconazole and itraconazole for treatment of rhinomaxillary mucormycosis

Rhinomaxiler mukorikozis tedavisinde flukonazol ve itrakonazolun karşılaştırılması

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Abstract

Aim: Rhinomaxillary mucormycosis (RMM) is a detrimental and progressive deep fungal infection which predominantly affects immunocompromised patients. The disease has heterogeneity in clinical manifestation and presents with unfavorable consequences. Despite recent advances in the diagnosis and treatment, the disease has inadequate prognosis overall. The aim of our study is to compare Fluconazole vs. Itraconazole for the management of RMM.

Methods: We retrieved demographic, clinical, radiological and histopathological data of patients affected with osteomyelitis in head and neck region and 33 patients exclusively affected with RMM were separated from departmental records. Several characteristics such as Gender, age, Diabetic status, co-morbidity were observed. Patients were randomly distributed in two groups with respect to the azole drug prescribed to them. Group A was given Fluconazole while group B was given Itraconazole. Aggressive surgery with concomitant use of antifungal drug was the mandatory treatment in all patients. Regular monitoring of side effects of drugs and recurrence was carried out for prolonged time.

Results: Overall, 18 patients were male and 15 patients were female with a ratio of M:F 1.2. Mean age of patients was 48.21 (11.66) with the age range from 25 years to 70 years. Out of 33 patients, 30 of the patients (90.9%) were diabetic. Fifteen patients in Group A were managed with Fluconazole while 18 patients in group B were treated with Itraconazole. There was no statistically significant difference observed in most of the clinical signs and symptoms presented in both groups as $P>0.05$ except for bone necrosis ($P=0.381$). In group A, 4 patients exhibited recurrence (26.6%) while in group B, 5 (27.7%) patients presented with recurrence ($P=0.943$).

Conclusion: Aggressive surgical approach along with supportive antifungal medication remained the mainstay of the treatment. Between Fluconazole and Itraconazole there was no difference observed.

Keywords: Rhinomaxillary mucormycosis, Fluconazole, Itraconazole

Öz

Amaç: Rhinomaksiler mukormikoz (RMM), baskın olarak immün sistemi baskılanmış hastaları etkileyen, zararlı ve ilerleyici bir derin fungal enfeksiyondur. Hastalık klinik tezahürde heterojenliğe sahiptir ve olumsuz sonuçlar doğurmaktadır. Çalışmamızın amacı, RMM tedavisi için Fluconazole - Itraconazole uygulamasını karşılaştırmaktır.

Yöntemler: Baş ve boyun bölgesinde osteomiyelit ile etkilenen hastaların demografik, klinik, radyolojik ve histopatolojik verilerini aldık ve sadece RMM'den etkilenen 33 hasta bölümsel kayıtlardan ayrıldı. Cinsiyet, yaş, diyabetik durum, komorbidite gibi çeşitli özellikler kaydedildi. Hastalar, kendilerine verilen azol ilacı açısından rastgele iki gruba ayrıldı. A grubuna Flukonazol, B grubuna Itrakonazol verildi. Antifungal ilacın birlikte kullanılması ile yapılan agresif cerrahi, tüm hastalarda zorunlu tedavi idi. İlaçların yan etkilerinin düzenli olarak izlenmesi ve tekrarlama uzun süre takip edildi.

Bulgular: Toplamda 18 hasta erkek, 15 hasta kadındı (E/K 1,2). Hastaların yaş ortalaması 48.21 (11,66), yaşları 25 ile 70 arasında değişmekteydi. 33 hastanın 30'u (%90,9) diyabetikti. Grup A'da 15 hasta Fluconazole ile tedavi edilirken, grup B'de 18 hasta Itraconazole ile tedavi edildi. Kemik nekrozu dışında her iki grupta da sunulan klinik belirti ve semptomların çoğunda $P>0,05$ düzeyinde istatistiksel olarak anlamlı bir fark bulunmadı ($P=0,381$). Grup A'da 4 hastada nüks görüldü (%26,6), grup B'de ise 5 hastada (%27,7) nüks saptandı ($P=0,943$).

Sonuç: Destekleyici antifungal ilaçlar ile birlikte agresif cerrahi yaklaşım tedavinin dayanak noktası olarak kaldı. Flukonazol ve Itrakonazol arasında anlamlı bir fark gözlenmedi.

Anahtar kelimeler: Rhinomaksiler mukormikoz, Flukonazol, Itrakonazol

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Introduction

Rhinomaxillary mucormycosis (RMM) is an angioinvasive fungal infection with high mortality rate [1]. It is caused by saprophytic filamentous organism, which belongs to the family Mucoraceae, class Phycomycetes of order Mucorale [2,3]. Mucormycosis has wide spectrum of clinical forms as cutaneous, rhinocerebral, rhinomaxillary, pulmonary, gastrointestinal and disseminated fatal infection [4]. However, the majority of the cases affecting the craniofacial region are rhino-orbito-cerebral Mucormycosis having incidence of 30-50% of all reported cases [4,5]. RMM is a fulminating opportunistic infection, particularly documented in immunocompromised patients with diabetes mellitus, neutropenia, malignancy, chronic renal failure and organ transplant patients [6]. However, it is seldom found in HIV positive patients [7]. The most common pathway of spread of RMM is inhalational, thereby affecting sinuses and respiratory tract [7]. Rarely, it has been reported in healthy immunocompetent patients with trauma, burn and surgery with infection spreading through cutaneous pathway [6,8]. Eminent serum level of unbound iron raises probability of mucormycosis because iron is the essential virulence factor for the fungi [9]. RMM originates from nasal or oral mucosa, extends to paranasal sinuses, orbit and cerebrum [10]. Patients with extensive disease present with headache fever, proptosis, sinusitis, ocular pain, vision loss, nasal discharge and palatal eschar [4,5,9]. Reported literature shows age range of 5–65 years with mean age of 39.9 (20.3) years, age range of 18 to 70 years with a mean of 47.3 (14.4) years and mean age of 50.7 (19.9) years. [5,6,9].

Early diagnosis is the crucial factor for prognosis of the disease because of its devastating nature. Clinical examination, Computerized Tomography (CT) scan or Magnetic resonance imaging (MRI) scan facilitates the presumptive diagnosis. Definitive diagnosis requires biopsy for histopathological evidence of aseptate hyphae with branches at right angle [10]. Primary treatment includes aggressive surgical debridement with prompt antifungal drug like amphotericin B, Fluconazole, Itraconazole, Posaconazole or Voriconazole. Additional supportive therapy includes iron chelators, caspofungin and hyperbaric oxygen [11]. Although, the standard antifungal therapy is parenteral infusion of amphotericin B but it has a disadvantage of prolonged hospitalization and need for regular monitoring because of its significant side effects [12]. Injection site allergic reaction requires administration of diphenhydramine [12]. Hence there was a need of alternative medication with minimal side effects and equal efficacy. So in our study we compared the efficacy and safety of fluconazole vs. Itraconazole for management of RMM. Alternative antifungal treatment includes use of azoles, preferentially Posaconazole [13].

Materials and methods

Case files of all the patients diagnosed with mucormycosis from January 2015 to December 2016 were retrieved from the departmental record. History, demographic data, clinical data, radiographical findings, histopathological analysis, treatment given and post-op results were collected. All patients, irrespective of age and gender who were diagnosed clinically, radiologically and histopathologically as having RMM were evaluated in the study. Patient suffering from Mucormycosis of maxillofacial region were included in the study, patients having bone necrosis, osteomyelitis or sinusitis for reasons other than Mucormycosis were excluded from the study.

Clinical diagnosis was completed on the basis of diverse signs and symptoms including necrotic palatal eschar, nasal obstruction, and tooth mobility, proptosis and vision loss. Radiological evidence (Figure 1) represented erosion of maxillary sinus wall, opacification of paranasal sinus, altered air/fluid levels of sinus, necrosis of dentoalveolar segment and extension beyond sinus to orbit. Histopathology on biopsy sample showed broad and irregular non septate hyphae which branches at right angle.

After the confirmation of diagnosis, antifungal medication was started and meanwhile the patient was prepared for surgical debridement. Preoperative antifungal was prescribed prior to surgery and post-operative antifungal was given to patients for 3 months. Patients were randomly allocated into two groups. In Group A, patients were managed with 150 mg fluconazole BD for 1 month and OD for 2 months while patients in Group B were prescribed Itraconazole 100mg BD for 1 month and OD for 2 months. During the treatment and postoperative period, patients were monitored clinically and radiologically for recurrence. Regular blood tests including serum urea and creatinine, electrolytes, liver function tests and renal function tests were conducted at regular intervals to monitor side effects of azole drugs. The results obtained of both groups were compared for efficacy, potency and side effects. All the patients were followed up for evaluation of recurrence. Surgical debridement remained the definite treatment. Rehabilitation in successful cases was carried out with maxillary obturators.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software (IBM SPSS v20.0, IBM Corporation, Armonk, NY, USA) was used to analyze the data. Frequency, percentages, means and standard deviations were calculated for different qualitative and quantitative variables. Patients were divided into two groups with respect to antifungal medication. Variables in both the groups were compared with chi-square test and *P*-value of <0.05 was considered as statistically significant.

Results

A total of 33 individual cases of RMM were analyzed and divided into two groups with reference to antifungal medication provided to them. Group A included 15 patients treated with fluconazole. Group B comprised of 18 patients treated with Itraconazole. Clinical site involved was Maxilla, with 14 (42.4%) of the cases affecting the left maxilla, 12 (36.4%) affecting right maxilla and 7 (21.2%) of the cases were bilateral. Diabetes mellitus (DM) was associated with RMM in 30 of the cases (90.9%) evaluated in our statistical analysis. Out of these, 7 (21.2%) diabetic patients were controlled and 23 (69.7%) had uncontrolled DM (Table 1).

Out of all 33 patients with mucorale infection, 12 patients (36.4%) had co infection of hepatitis. In Group A, 5 were females and 10 were males (M: F 2:1), age range was from

26yr to 65 year with a mean of 42.8 (9.27) years. In Group B, 10 were females and 8 were males (M:F 1:1.25), age range was from 25yr to 70 year with mean age 52.72 (11.19). Generalized symptoms of fever, headache and lethargy were diagnosed in all cases in both groups. Overall, common clinical features were nasal obstruction (93.9%) and midface bone necrosis (87.9%). Out of 33 patients, Palatal eschar was present in 25 patients (75.8%) as shown in Figure 2. Clinical symptoms observed in both groups are shown in Table 2.

There was no statistically significant difference observed in all clinical signs and symptoms presented in both groups as p>0.05 except for bone necrosis (P<0.05). No statistics of Nasal obstruction was calculated because it was a constant clinical feature in both groups.

Surgical debridement combined with the pre-operative and post- operative antifungals was the principal treatment. Fluconazole was given to 15 patients in Group A and Itraconazole was given to 18 patients in Group B. Surgical management and recurrence in both groups is described in table 3.

After maxillectomy (figure 3), patients were monitored for prognosis and success. Maxillary obturators were given to all patients after aggressive surgical approach as shown in figure 4. Overall, 27.27% or 9 cases in both groups exhibited recurrence as shown in table 3. The chi square results of recurrence in both groups illustrated value of P=0.943, hence there was no remarkable difference in the results. RMM was the independent predictor of death with mortality rate of 3%. Mean follow up period was 29.33 (5.69) months.

Table 1: Diabetic status of the patients

Diabetic status	n	%
Absent	3	9.1
Controlled Diabetes	7	21.2
Uncontrolled Diabetes	23	69.7

Table 2: Clinical symptoms of both groups

Clinical symptoms	Group A		Group B		*P*-value
	n	%	n	%	
Proptosis	4	26.67	6	33.3	0.678
Partial Vision Loss	3	20	4	22.2	0.982
Complete vision loss	1	6.67	1	5.5	0.982
Eschar	11	73.3	14	77.7	0.767
Pus discharge	12	80	13	72.2	0.604
Tooth mobility	11	73.3	13	72.2	0.943
Nasal obstruction	15	100	18	100	_
Bone necrosis	14	93.3	15	83.3	0.381
Nerve Involvement	5	33.3	6	33.3	1.0

Table 3: Surgical management and recurrence in both groups

	Group A		Group B	
	n	%	n	%
Partial maxillectomy	10	66.6	11	61.1
Total maxillectomy without involving orbit	2	13.3	3	16.6
Total maxillectomy with involving orbit	3	20	4	22.2
Recurrence	4	26.6	5	27.7

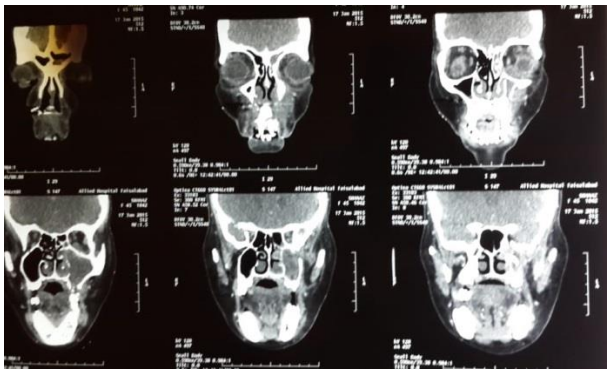

Figure 1: Computed tomography scan showing involvement of left maxillary sinus and nasal cavity

Figure 2: Palatal necrosis/eschar in a patient affected with rhinomaxillary mucormycosis

Figure 3: Intraoral photograph of total maxillectomy

Figure 4: Maxillary Obturator for the patient after total maxillectomy

Discussion

RMM is an aggressive fungal disease with threatening consequences. It is non-contagious infection of nose, maxilla, sinuses and orbit which spreads through inhalational spongiospores in air or via direct mucosal contact in susceptible individuals [5]. It extends from paranasal sinuses and rapidly progress to involve orbit causing proptosis, vision impairment and blindness [14,15]. This retrospective study enabled assessment of RMM cases in terms of clinical signs, management, recurrence and fatality. Patients were distributed in two groups with respect to antifungal medication given to them for 3 months.

In our study, 18 out of 33 patients were male (54.5%), while 15 patients were female (45.4%), with ratio of M: F 1.2:1. This data is comparable to clinical study done by Carlos et al [5]. Notably in our study, 30 out 33 patients (90.9%) had diabetes as a predisposing factor. This strong correlation between RMM and Diabetes mellitus in our study is similar to data collected in different series [16-18]. Majority of the patients had uncontrolled diabetes but with the help of medical practitioners the blood sugar level of patients was brought under control by placing them on insulin. Diabetic ketoacidosis is a significant risk factor because fungi produces ketoreductase enzyme to utilize ketone bodies for growth [19].

Clinically, all affected patients presented with fever, headache and sinusitis. Overall, in both groups common signs

and symptoms observed were eschar formation (75.8%), pus discharge (75.8%), tooth mobility (72.7%), nasal obstruction (100%) and bone necrosis (87.9%). The most adverse clinical feature was complete vision loss reported in 2 patients (6.1%). In our study, Intranasal and palatal eschar was the most frequent finding (75.9%) as compared to a retrospective study which mentions incidence of 40-50% only [16].

Essential aids for the management of disease included detailed history, clinical and cranial nerve examination, CT scans, blood tests and biopsy of the lesion. Acknowledged treatment measures consist of aggressive surgical debridement and antifungal medication like amphotericin B, Fluconazole, Itraconazole, Posaconazole and Voriconazole. In our study treatment regimen consisted only of Fluconazole and Itraconazole for 3 months. Group A received Zolanix (fluconazole) 150mg BD for one month, followed by OD dose for two months. Group B was administered Itraconazole (ICON) 100mg BD for one month, followed by OD dose for two months. A total expense of 3 month regimen for fluconazole was PKR 11,970 ($103.54) and total cost of ICON 3 month regimen was PKR 6,150 ($53.20). During the treatment, Patients were monitored for liver function tests, renal function tests, urea and creatinine and blood electrolytes.

Common side effects of azoles include abdominal distress, headache and pruritus. Generally, amphotericin drug is preferred in terms of efficacy but there are certain limitations because of its potential side effects [21]. Caitlin et al emphasize on the improved efficacy of amphotericin in combination with caspofungin, compared to monotherapy [22]. There is increased risk of nephrotoxicity in patients managed with amphotericin for long term, hence there is need for regular renal function assessment and monitoring for hypokalemia, hypomagnesaemia and metabolic acidosis [23,24]. Its proven nephrotoxicity may require withdrawal of the treatment despite fatal fungal infection [24]. Atahan et al. [25] mentions prolonged duration of 6 months treatment with amphotericin followed by oral fluconazole. Furthermore patient requires hospital administration and parenteral infusion at dose of amphotericin 1-1.5 mg per kg because of limited GIT absorption and bioavailability [26]. In addition to this amphotericin infusion is associated with injection site irritation, swelling and pain. It is also known to cause tachypnea 1-3 hours after infusion.

On the contrary, azoles have sufficient oral bioavailability therefore it can safely be administered orally. Fluconazole has >90% bioavailability and Itraconazole has 55% bioavailability [27]. Since no parenteral injection is required; it is advantageous with regard to patient comfort. Furthermore, azoles are not strongly correlated with deranged renal function tests and raised urea and creatinine as compared to nephrotoxic amphotericin. Another benefit of Fluconazole is its availability in IV formulation as well for patients who are unable to take oral medication. In our study, none of the patients presented with side effects severe enough warranting withdrawal of the drug. However, Itraconazole is associated with weight gain [28]. Posaconazole and voriconazole were not included in our management plan because of lack of availability in our setup and high cost. In addition to this, deferasirox iron chelating agent is considered as salvage therapy for progressive mucormycosis [29]. However it was not used in our study.

Overall, there was no significant difference observed in potency, efficacy and safety in both groups. The azoles were used preoperatively and post operatively with intensive surgical debridement of devitalized tissue in all patients. Aggressive surgical management remained the mainstay of treatment required to eradicate the fungus affected necrotic tissue. All patients were kept on follow up and recurrence was addressed immediately. There were total of 9 cases of recurrence of which 4 belonged to Group A and 5 were in Group B. One patient in group 2 succumbed to disease after recurrence. Maxillary obturators were used as permanent rehabilitation option because uncontrolled diabetes is a poor indicator for successful bone grafting and implants.

Insignificant results were obtained owing to a relatively small sample size. Future studies with a larger population are recommended in order to achieve significant results.

Conclusion

RMM is the debilitating fungal infection which requires surgical approach and early medical intervention to improve the prognosis. Immunocompromised patients, particularly uncontrolled diabetics impose the significant risk in acquiring the disease. In our study, Fluconazole and Itraconazole showed no differences in recurrence and presentation of clinical signs and symptoms except for the bone necrosis. Therefore, the extensive surgical debridement is the mainstay of the treatment with adjunctive treatment with antifungal medications.

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Assessment of age- and sex-dependent changes of cerebellum volume in healthy individuals using magnetic resonance imaging

Sağlıklı bireylerde cerebellum hacminin yaş ve cinsiyete bağlı değişiminin manyetik rezonans görüntüleriyle değerlendirilmesi

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Abstract

Aim: Cerebellum is a structure ingrained in fossa cranii posterior and has a great role in contributing to the coordination of motor functions, regulation of muscle tone, and motor learning, as well as precision and accurate timing. This study primarily aimed to establish a cerebellum measurement scale based on age and sex.

Methods: The study was carried out with the approval of Adiyaman Clinical Research Ethics Board and the contributions of Adiyaman University Training and Research Hospital Radiology Department. The data were retrospective cohort study obtained from the magnetic resonance images of 160 individuals (80 female and 80 male). The individuals included in the study were divided into age groups of 0-4, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59 and 60-80 years, each consisting of 10 women and 10 men. All statistical analyses were performed using SPSS program.

Results: The cerebellum volume was 139.23 (11.73) cm^3 for women and 151.14 (12.30) cm^3 for men aged 10-19 years, and the difference was significant (P=0.040). The cerebellum volume of individuals aged 0-4 years was found to be 105.05 (33.28) cm^3 with a significant difference compared to the remaining age groups (P<0.001). The total cerebellum volume was calculated as 128.84 (29.66) cm^3 for individuals aged 0-17 years and 141.91 (15.06) cm^3 for those in the 18-80 years group. It was found to be smaller in the 0-17 age group (P<0.001).

Conclusion: Determining the volumes of brain parts in healthy individuals is very important in assessing the aging process, as well as contributing to the differentiation of normal and pathological conditions.

Keywords: Cerebellar volume, Magnetic resonance imaging, Age, Gender

Öz

Amaç: Serebellum fossa cranii posterior'da yerleşmiş, motor fonksiyonların koordinasyonu, kas tonusunun düzenlenmesi ve motor öğrenmede; ayrıca hassasiyet ve doğru zamanlamanın sağlanmasına katkıda bulunan beyinde önemli rolü olan bir yapıdır. Bu çalışma ile amacımız öncelikle yaşa ve cinsiyete bağlı olarak serebellum ölçüm skalası oluşturabilmektir.

Yötemler: Çalışma Adıyaman Klinik Araştırmalar Etik Kurulu'ndan alınan onay ile Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Radyoloji Anabilim Dalı'nın katkılarıyla gerçekleştirilmiştir. Veriler manyetik rezonans görüntüleme yöntemi kullanılarak (80 kadın ve 80 erkek) toplam 160 bireye ait görüntüler üzerinde retrospektif kohort bir çalışma olarak elde edilmiştir. Çalışmaya dâhil edilen bireyler 0-4 yaş, 5-9 yaş, 10-19 yaş, 20-29 yaş, 30-39 yaş, 40-49 yaş, 50-59 yaş ile 60-80 yaş toplam 8 gruba ayrılmış ve her yaş grubu da 10 kadın ve 10 erkek toplam bireylerden oluşmaktadır. Elde edilen verilerin istatistiksel tüm analizleri için SPSS programı kullanılmıştır.

Bulgular: Çalışmamızda serebellum hacmi 10-19 yaş kadınlarda 139,23 (11,73) cm^3 ve erkeklerde 151,14 (12,30) cm^3 idi (P=0,040). 0-4 yaş arası bireylerin serebellum hacmi 105,05 (33,28) cm^3 diğer yaş gruplarına göre daha küçük bulundu ve diğer gruplar ile arasında anlamlı bir farklılık vardı (P<0,001). 0-17 yaş arasındaki bireylerde toplam serebellum hacmi 128,84 (29,66) cm^3,18-80 yaş grubundaki bireylerde toplam serebellum hacmi 141,91 (15,06) cm^3 idi. 0-17 yaş grubunda daha küçük bulundu (P<0,001).

Sonuç: Beyin bölümlerinin sağlıklı bireylerdeki hacimlerinin belirlenmesi; normal ve patolojik durumların ayırt edilmesine katkı sağlamakla birlikte yaşlanma sürecinin değerlendirmesinde de oldukça önemlidir.

Anahtar kelimeler: Serebellar hacim, Manyetik rezonans görüntüleme, Yaş, Cinsiyet

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Introduction

Cerebellum, the second largest part of the encephalon and the largest part of the rhombencephalon [1], is ingrained in the fossa cranii posterior and has important functions for the brain, contributing to the coordination of motor functions, regulation of muscle tone, and motor learning, as well as precision and accurate timing [2]. The external structure of the cerebellum consists of two lateral lobes known as hemispheres and a medial part called vermis cerebelli that connects these lobes [3]. In the median sections of the cerebellum composed of white matter on the inside and gray matter on the outside are corpus medullare cerebelli and the surrounding cortex cerebelli, referred to as arbor vitae (tree of life) since the structure resembles the branches of a tree [2].

Changes in the cerebellum volume are seen in many diseases in the clinic, especially occurring due to neuropsychiatric, neurological, hereditary-idiopathic, developmental, vascular and metabolic diseases, nutrition and infection-related diseases, and physical trauma [4]. Therefore, the total volume and volume ratios are frequently used in experimental studies, as well as in clinical diagnosis, treatment and treatment planning [5].

Stereology, which is now considered to be one of the most reliable methods used to measure the volume of irregularly shaped objects, is a branch of science that provides many numerical values related to a structure, such as the volume and surface area based on two-dimensional sections or section images of that structure [6]. Taking advantage of soft tissue contrast analysis [7], the images obtained by magnetic resonance imaging (MRI), which does not contain ionizing radiation that is harmful to tissues, have an important place in the diagnosis of many neurological and psychiatric diseases and revealing intracranial anatomical structures and pathological changes [8].

In this study, we divided healthy individuals into age groups and measured cerebellum volumes on MRI images using stereology. We consider that this will provide useful data to guide clinicians in the diagnosis, treatment, and monitoring treatment progress in the clinic, as well as pioneering further studies.

Materials and methods

The study was carried out with the approval of Adiyaman Clinical Research Ethics Committee, and the measurements were undertaken by two specialist radiologists with more than 10 years of experience in the Radiology Department of Adiyaman University Training and Research Hospital.

The data were retrospectively obtained from the images of 160 individuals, 80 female and 80 male, recorded in the radiology archive of the hospital. No age limitation was used for the individuals included in the study. For the evaluation, the sample was divided into eight age groups as 0-4 years, 5-9 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, and 60-80 years, each containing 20 people (10 female and 10 male).

Included in the study were patients who underwent cranial MRI and were reported to have normal findings. The patients who presented to the hospital due to cardiovascular diseases, neurological diseases, psychiatric diseases, thyroid, transient ischemic attacks, tumor, seizures, dementia, and diabetes were excluded. The parameters used in the MRI and radiological measurements were age, gender, section thickness, section number, surface area, and cerebellum volume.

Imaging technique and volume measurement

MRI imaging was performed using the Philips Achieva 1.5 Tesla (Achieva; Philips Medical Systems, Best, the Netherlands) system, which allows soft tissue analysis. The same protocol was used for the assessment of all MRI data. For the calculation of cerebellum volume, T2-weighted axial images (TR: 4800, TE: 100, slice thickness: 5 mm, FOV: 230, average: 1, matrix: 208x130) were recorded. The volumetric measurements were obtained based on the contour stack principle using MPR View 3D workstation. Cerebellar volume calculations were performed planimetrically according to Cavalieri's principle (Figure 1).

Figure 1: Volumetric measurement of the cerebellum (shown in red) on a T2-weighted image in the axial plane. The fourth ventricle was not included in the volumetric calculation.

Statistical analysis

Statistical analysis was performed using the SPSS program v. 15.0. Conformance of quantitative variables to normal distribution was evaluated using one-sample Kolmogorov Smirnov test. The independent two-sample t-test was employed for the comparison of two independent groups and the analysis of variance for more than two groups. For the variables found significant, Tukey's Honest Significant Difference binary comparison test was utilized to determine the differences between the groups. The results were given as mean (standard deviation). The minimum level of significance was considered $P<0.05$.

Results

The cerebellar volume of males at 10-19 age group has been detected significantly higher than females ($P=0.004$). For the other age groups the cerebellum volume is higher at males but not significant. Table 1 shows the relationship between age and gender and the mean cerebellar volume calculated using the planimetric method (Figure 2).

In the 0-4 year old group, the total cerebellum volume was found to be 105.05 (33.28) cm^3, which was lower compared to the remaining age groups ($P<0.001$). Table 2 presents the relationship of the mean cerebellum volume with age groups.

The cerebellar volume of the individuals in the 0-17 age group was found to be significantly smaller than that of the 18-80 age group ($P<0.001$) (Table 3).

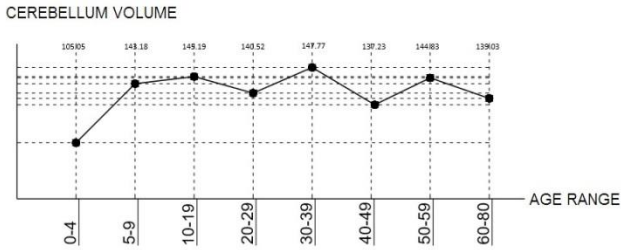

Figure 2: Changes in cerebellum volume according to age groups

Table 1: The relationship of cerebellum volume with age and gender

	Gender	Mean (SD)	*P*-value*
0-4 Years	Female (n = 10)	91.70 (38.55)	0.071
	Male (n = 10)	118.40 (21.34)	
5-9 Years	Female (n = 10)	137.40 (13.83)	0.263
	Male (n = 10)	144.82 (14.84)	
10-19 Years	Female (n = 10)	139.23 (11.73)	0.040
	Male (n = 10)	151.14 (12.30)	
20-29 Years	Female (n = 10)	140.12 (15.90)	0.870
	Male (n = 10)	141.46 (19.83)	
30-39 Years	Female (n = 10)	145.94 (17.15)	0.419
	Male (n = 10)	151.78 (14.31)	
40-49 Years	Female (n = 10)	132.29 (14.99)	0.107
	Male (n = 10)	142.16 (10.68)	
50-59 Years	Female (n = 10)	138.67 (17.20)	0.122
	Male (n = 10)	150.99 (16.69)	
60-80 Years	Female (n = 10)	133.29 (17.13)	0.148
	Male (n = 10)	144.77 (16.82)	

SD: Standard deviation, *: Independent two-sample t-test

Table 2: The relationship of cerebellum volume with age groups

Age Groups	Mean (SD)	*P*-value*
0-4 Years (n = 20)	105.05[b] (33.28)	<0.001
5-9 Years (n = 20)	143.18[a] (10.15)	
10-19 Years (n = 20)	145.19[a] (13.20)	
20-29 Years (n = 20)	140.52[a] (13.31)	
30-39 Years (n = 20)	147.77[a] (13.39)	
40-49 Years (n = 20)	137.23[a] (13.65)	
50-59 Years (n = 20)	144.83[a] (17.66)	
60-80 Years (n = 20)	139.03[a] (17.54)	

SD: Standard deviation, *: One-way variance analysis, [ab]: The letters in the same column (a-b) refer to the significant differences ($P<0.05$) between the means according to the results of Tukey's Honest Significant Difference test.

Table 3: Cerebellum volume according to the age groups of below and above 18 years

Age Group	Mean (SD)	*P*-value*
0-17 Years (n = 51)	128.84 (29.66)	<0.001
18-80 Years (n = 109)	141.91 (15.06)	

SD: Standard deviation, *: Independent two-sample t-test

Discussion

The various anatomic and physiological changes beginning with the birth of an organism and continuing with aging throughout the life span have attracted the attention of many researchers [9]. The volumes of the brain and its sections in healthy individuals are important in the evaluation of both the clinical pathological condition and the normal aging process [10]. In addition, it has been demonstrated that there is a volumetric decrease in brain tissue and cerebellar atrophy occurs with aging [11,12]. Calculation of the cerebellum volume is important to accurately assess size differences that may later occur and calculate the changes [9].

The volume of intracranial structures can be measured by using different techniques. Similarly, in the current study, the cerebellum volume measurements were undertaken using planimetry in accordance with Cavalieri principle. In planimetry, the boundaries of structures of interest on sectional images are manually drawn for each section individually in the electronic environment. The sum of the measured cross-sectional areas is multiplied by section thickness to obtain the volume of the structure [13,14].

Knickmeyer et al. [15] found the volume of cerebellum to be 91.962 cm^3 in one-year-olds and 105.154 cm^3 in two-year-old. In our study, the cerebellum volume was calculated as 91.70 (38.55) cm^3 for girls and 118.40 (21.34) cm^3 for boys aged 0-4 years, with a mean of 105.05 (33.28) cm^3. In the literature, the measurements of cerebellar hemispheres, transcerebellar diameter, and anterior-posterior dimension in individuals aged 0-4 years were previously reported [16]. However, we did not find an enough studies on the cerebellar volumes of different age groups; thus, we consider that there is a need for further research in this area.

In many studies it has been observed that the cerebellum volume of males is higher than females for all age groups [17]. It was reported that men had a larger cerebellum than women of the same age, and these differences might also reflect sexual dimorphism in the body structure [18]. Cerebellum volume of males has been calculated as higher than females in this study too for all age groups. But these differences are not statistically significant except for 10-19 age group.

Mas [19] has been stated that cerebellar volume is greater in males than in females between the ages of 10-19 years. Similarly, it has been determined that the cerebellar volume was greater in males than in females in the 10-19 age group in this study. It has been considered that this difference may be associated with the hormones released in adolescence.

Comparative studies investigating the volume of the cerebellum may constitute valuable references for other research demonstrating physiological and pathological conditions, and cerebellum volumes in different races [20,21]. Mas [19] performed the volumetric analysis of cerebrum-diencephalon, cerebellum and total intracranial structures using the MRI method in a healthy sample consisting of 42 male and 42 females aged 10 to 86 years according to gender and decade and found a significant volumetric decrease in these structures with increased decades. He noted that the cerebellum volume did not significantly differ between men and women at the age of 60 years or older, with the latter having a smaller cerebellum for each decade. In another study, Woodruff-Pak et al. [22] investigated age-related cerebellar volume changes in healthy subjects and found no relationship between age and cerebellar volume. Luft et al. [23] investigated the effects of age on cerebellar volume using the MRI images of 48 volunteers aged 19.8-73.1 years. The results revealed that the total cerebellar volume remained constant until the age of 50 and showed a linear decrease after this period. Many studies investigating age-dependent changes in cerebellum volume provide controversial results. Some researchers detected a decrease in cerebellum volume with aging [17], while others reported no significant decrease in older groups [24]. In the current study, we found that the cerebellum volume was smaller in the 0-4 years group, but there was no significant change in the remaining age groups. Furthermore, women aged 60 to 80 years had a smaller cerebellum than men in the same age group, but the difference was not statistically significant. However, since the gaps between the cerebellar sulci were included in the total volume calculation, further studies are needed to perform measurements by considering sulcal dilatations that develop in the background of early-stage atrophy, especially after the age of 60 years.

This study has certain limitations. The first is the retrospective design; i.e., retrospective collection of data. The

second limitation concerns the relatively small number of cases and radiological analyses being undertaken by a single radiologist. In addition, the ages at which adolescence began and individuals reached adulthood were not known. Lastly, the parameters that can change the hormonal status of women of reproductive age, such as the number of births and breastfeeding period were not investigated.

Conclusion

Cerebellum volume of males has been found to be significantly higher than females for all age groups. Furthermore, it has been found lower in the 0-4 age group when compared to the other age groups. In the 10-19 age group, the cerebellum level of males has been observed considerably higher when compared with females, this phenomenon may be related with the adolescence period hormonal changes.

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The effects of epidural bupivacaine administration for postoperative pain after major abdominal surgery

Majör abdominal cerrahide epidural bupivakain uygulamasının postoperatif ağrı üzerine etkileri

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Abstract

Aim: Postoperative pain is a major problem after major abdominal surgery and conventional intramuscular analgesic therapy is usually not enough. We investigated the effectiveness and timing of epidural patient control analgesia on intraoperative analgesic consumption and postoperative pain, after major abdominal surgery.

Methods: We studied 41 patients prospectively. This was a prospective cohort study. The patients, after ethics committee approval, who were planned to have major abdominal surgery, aged between 35 and 75, were included to the study. 37 patients' data were included to the study; because two patients were excluded because of motor block developed during research, and 2 patients were excluded because catheter tips were migrated from the epidural space. Epidural catheters were applied to all patients, at proper levels for the surgery, preoperatively. In the first group; bupivacaine infusion was administered postoperatively, via patient controlled analgesia (PCA) machine. In the second group 25 mg bupivacaine bolus was administered before surgery and bupivacaine infusion via PCA was administered at the postoperative period. In the third group 25 mg bupivacaine bolus was administered preoperatively and bupivacaine infusion was administered intra and postoperatively via PCA. Pain levels of the patients were evaluated by using numeric rating scale (NRS). In NRS, patients were asked to evaluate their pain levels between 0 to 10, as 0; no pain and 10 is the worst pain ever.

Results: In all groups postoperative NRS levels were below 4, and sufficient postoperative analgesia was provided. In the third group significant lower analgesia scores and lower intraoperative analgesic consumptions were achieved (P<0.05). In this group arterial blood pressures were lower than the other groups, but they were not lower than the physiologic limits.

Conclusion: Epidural bupivacaine administration is a safe and effective method for postoperative pain management for patients who will have major abdominal surgery.

Keywords: Epidural analgesia, Bupivacaine, Major abdominal surgery

Öz

Amaç: Majör abdominal cerrahi sonrası, postoperative analjezi önemli bir problemdir ve konvansiyonel intramüsküler analjezik tedavisi genellikle yetersizdir. Biz bu çalışmada, majör abdominal cerrahide, hasta kontrollü epidural analjezi uygulanım zamanının ve şeklinin, intraoperatif analjezik ihtiyacı ve postoperatif ağrı üzerine etkilerini araştırdık.

Yöntemler: 41 hasta prospektif olarak çalışıldı. Bu, prospektif kohort bir çalışmadı. Elektif majör abdominal cerrahi uygulanacak yaşları 35-75 arasında değişen 41 hasta etik komite izni alınarak çalışmaya dahil edildi. Motor blok gelişmesi sebebiyle iki hasta ve epidural kateterin yerinden çıkması sebebiyle iki hasta çalışmadan çıkarıldı. 37 hastadan elde edilen veriler değerlendirmeye alındı. Bütün gruplara preoperatif, cerrahiye uygun dermatomda blok oluşturacak şekilde epidural kateter takıldı. 1. gruba bupivakain infüzyonu postoperatif dönemde hasta kontrolü analjezi (HKA) aleti ile uygulandı. 2. gruba cerrahi başlamadan 25 mg bupivakain bolus uygulamasının ardından postoperatif HKA aletine bağlandı. 3. gruba ise cerrahi öncesi 25 mg bupivakainin bolus uygulamasının ardından intraoperative ve postoperative dönemde HKA aleti ile bupivakain uygulandı. Hastaların ağrı düzeyleri "numeric rating scale (NRS)" ile değerlerlendirindi. NRS'de hastalara, 0: hiç ağrı yok, 10: bugüne kadar hissedilen en şiddetli ağrı olacak şekilde, ağrılarına 1 ile 10 arasında bir değer vermeleri istendi.

Bulgular: Bütün gruplarda NRS değerleri 4'ün altındaydı ve yeterli analjezi sağlandı. 3.grupta, diğer gruplara göre anlamlı olarak daha düşük ağrı skorları ve intraopertif analjezik tüketimi görüldü (P<0.05). Bu grupta, fizyolojik sınırlar içinde olmakla beraber, daha düşük kan basıncı değerleri gözlendi.

Sonuç: Bu sonuçlar ile HKA ile epidural bupivakain, majör abdominal cerrahi uygulanacak hastalara, analjezik tedavisi olarak kullanılabilir.

Anahtar kelimeler: Epidural analjezi, Bupivakain, Majör abdominal cerrahi

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Introduction

Patients, who will have major abdominal surgery, need serious pain management at the postoperative period. Many trials revealed that, conventional pain management with intramuscular analgesics is insufficient for many patients [1,2]. For this reason, epidural analgesia and patient controlled analgesia have been in used for postoperative pain management recently. Epidural analgesia is a good choice for pain management and it has also some more advantages. Early gastrointestinal function improvement, less postoperative pulmonary complications, less myocardial ischemia incidence, better mobilization, less thromboembolism risk and less chronic pain syndromes are among these advantages [3]. When risks, costs and advantages of epidural analgesia are considered, this technique must be used in selected patients. Epidural analgesia is useful for patients who are expected to have serious postoperative pain and also have high risk for postoperative pulmonary complications.

Preemptive analgesia is described as an effective postoperative analgesia therapy, which blocks sensitization of central nervous system that causing increase of nociceptive perception [4]. Animal studies revealed that, pain therapy started before tissue trauma, is more effective for postoperative pain therapy [5-7]. But clinical studies showed weak positive or negative results [8-10].

In this study, we aimed to determine the effects local anesthetics administered from epidural catheter, on postoperative pain and analgesic consumption.

Materials and methods

After ethics committee approval, 41 patients from ASA II-III were enrolled to the study. The study was planned as a preliminary study so the number of the patients is low. After promising results we plan to continue the study. The study was planned as prospective, randomized and double-blinded. Patients who were planned for elective major abdominal surgery were enrolled to the study (Table 1). The patients who have contraindications for epidural catheterization, coagulation abnormalities, skin infection at catheterization site, local anesthetic allergies and serious renal or hepatic dysfunction were excluded from the study.

Patients were divided into three groups randomly. The patient's group was determined by choosing one of the sealed envelopes containing one of the group numbers. After the monitoring of blood pressure and heart rate, 0.07 mg/kg midazolam and 0.01 mg/kg atropine intramuscular were given for premedication. After 500 ml of colloid infusion, an epidural catheter was inserted from appropriate level for surgery, ranging thoracic 7 to 12, directing 4-6 cm cephaloid. The catheter was tested by 3 ml of 2% lidocaine, and then the patient was taken to the operation room.

In all groups, 4-6 mg/kg thiopental or 0.3 mg/kg etomidate, 0.1 mg/kg vecuronium and 1.5 mg/kg lidocaine were given for anesthesia induction. 50% N_2O and 0.8% MAC isoflurane mixture were given for anesthesia maintenance and vecuronium was given when needed. After anesthesia induction all patients were monitored with central venous catheter and urinary catheter. During operation, 0.5 mg alfentanil was added, if there were symptoms of inadequate anesthesia or analgesia. Total alfentanil dose was recorded.

In the first group (Group 1, n=12); 5 ml of isotonic solution was given from epidural catheter at the arrival to the operation room. After 20 minutes, anesthesia induction was given. At the end of the operation; at the postoperative care unit (PACU), the patients were monitored with noninvasive blood pressure, ECG and pulse oximetry (SpO_2). 10 ml of loading dosage, 5 ml infusion and 5 ml of bolus dose of 0.125% bupivacaine with 20 minutes lockout time, with a PCA (acute pain manager - APM, Abbot ®) was started right after. The patient's pain levels were evaluated with numeric rating scale (NRS). In NRS, patients were asked to evaluate their pain levels between 0 to 10, as 0; no pain and 10 is the worst pain ever. The NRS levels, total analgesic consumption, sedation level (0: fully awake, 1: arousable on calling, 2: arousable with painful stimulus, 3: no response) were evaluated by another anesthesiologist who does not know the patient's group, at 0^{th}, 30^{th}, 60^{th}, 90^{th}, 120^{th} minutes and 3^{th}, 4^{th}, 6^{th}, 12^{th}, 24^{th} and 48^{th} hours. Blood pressure levels, heart rates, respiratory rates, SpO2 levels and complications were recorded at the same time. If the patient's NRS level is higher than 4, additional 25 mg bupivacaine bolus was given from epidural catheter. Despite the additional dose, if the patient still had pain, the patient was excluded from the study and parenteral opioids were given for pain management. At postoperative 24^{th} hour, if the patient's NRS was 0 hasn't any complications, and then the patient was disengaged from PCA and transferred to the regular ward. If the patient had pain, 25 mg bupivacaine was given from the epidural catheter and recorded. At the regular ward, pain management continued with NSAI drugs, by the doctor in charge at the regular ward. At postoperative 48^{th} hour, if the patient had no pain the epidural catheter was withdrawn.

In the preoperative bolus group (Group 2, n=13), after the same premedication with group 1, epidural catheter was inserted. At the operating room, 25 mg bupivacaine bolus was given as loading dose, 20 minutes before anesthesia induction. Same anesthesia induction and maintenance was administered. Alfentanil was given during the operation if necessary and recorded. At the PACU, PCA was started in the same way, and pain management was started. Postoperative analgesic therapy and follows were recorded by a different anesthesiologist who is unaware of the patient's group.

In the intraoperative infusion group (Group 3, n=16), after epidural catheterization, 25 mg bolus bupivacaine was given and bupivacaine infusion via PCA was administered through operation. When the patient arrived to the PACU, bupivacaine consumption was recorded and the memory of PCA machine deleted. The patients were followed as the same way with the other groups, by a different anesthesiologist, at the postoperative period.

Statistical analysis

Data were analyzed with "One Way ANOVA" test for one way variance, by "SPSS 23.0 for Windows" computer program. Tukey test was used for differences between groups. $P<0.05$ value was accepted as significant.

Results

Demographic data, ASA classifications, operation times and operation types were similar between groups (Table 1, 2). There weren't any significant differences between heart rates at the postoperative period.

Arterial blood pressure values in the third group, at 60th minutes were lower than group 1 (P=0.028) and group 2 (P=0.016). And at 4th hour again in the third group, arterial blood pressure values were significantly lower than group 1 (P=0.032) and group 2 (P=0.024). Again in the third group, blood pressure at 30th minutes were lower than group 2 (P=0.021). And also at 90th minutes in the third group, arterial blood pressure levels were lower than group 2 (P=0.017) (Table 3). But these levels were within the physiologic range so we did not intervene. There weren't any significant differences between other blood pressure levels.

There weren't any differences between arterial oxygen saturation levels and respiratory rates between the groups. But one patient from the first group and two patients from second group, needed oxygen therapy via oxygen mask, since their SpO2 levels were below 90, at the early postoperative period. The patient's from the first group, NRS level during first two hours was 5 and sedation score was 1. The two patients' from the second group, NRS levels were 4 and sedation scores were 1. And in the intraoperative period, all these three patients received one mg alfentanil. This amount of alfentanil was higher than the mean levels of alfentanil consumption in all groups. After additional analgesic therapy and a complete recovery from anesthesia, SpO_2 levels were better and inhaler oxygen therapy was no longer needed.

There weren't any differences between sedation scores between the groups. All patients were lightly sedated in the early postoperative period.

Lower pain scores were recorded in group 3, according to the other groups (Table 4). NRS pain scores in group 3, at 30th, 60th, 90th, 120th minutes and at third, 4th, 6th, 12th and 24th hours were significantly lower than the other groups. There weren't any difference between the first and the second group. NRS scores were recorded as 5 in the first and second groups in the first 90 minutes postoperatively, after 90 minutes the NRS scores were below 4. At 48th hour, all patients' NRS scores were below 2 and none of them needed analgesic therapy any more.

There weren't any significant differences between bupivacaine consumption between the groups.

Two patients from the third group received 25 mg of bupivacaine boluses from epidural catheter, because NRS scores were above 4. Since these patients' pain levels didn't change after the boluses of bupivacaine, the patients were excluded from the study, assuming that the epidural catheters were migrated from the epidural space. Parenteral opioids were used for the rest of their pain management.

Intraoperative alfentanil consumption was significantly lower in the third group, then the other two groups (P=0.012). Mean values of intraoperative alfentanil consumption was 0.42 (0.37) mg in the first group, 0.31 (0.40) mg in the second group and 0.02 (0.2) mg in the third group. Also in the third group patients' intraoperative isoflurane consumption was lower. Since study protocol didn't include isoflurane consumption, we couldn't assess it properly.

Postoperative nausea and vomiting was detected in one patient from the first group and one patient from the third group. They were successfully treated with 10 milligrams of metoclopramide.

Partial motor blockage at one extremity was observed at 3 patients from group 2 and three patients from group 3. Bupivacaine infusions were paused and epidural catheters were withdrawn 2 centimeters back. After the resolving of motor blockage, the epidural catheter was checked again and bupivacaine infusion was started. But, one patient from group 2 and three patients from group 3, developed motor blockage again, so they were excluded from the study. Epidural catheters were removed and parenteral opioids were used for the rest of their pain management.

In this trial, none of the patients developed complications like epidural hematoma, epidural abscess, pruritus or neurologic damage. Urinary retention was not observed because all patients were urinary catheterized for 24 hours postoperatively.

Table 1: Type of operation and number of patients

	Group 1	Group 2	Group 3
Total gastrectomy	4	5	4
Subtotal gastrectomy	1	2	0
Whipple	2	1	2
Hepatic cyst hydatid	0	0	2
Biliodigestive bypass	1	2	1
Esophagectomy	1	0	0
Colon resection	2	1	2
Palliative bypass	1	1	2

Table 2: Demographic data of the patients

	Group 1	Group 2	Group 3	*P*-value
n	12	12	13	
Age (year)	64.2 (9.1)	56 (14.6)	55 (16)	0.101
Height (cm)	169 (3)	167 (4)	170 (2)	0.086
Weight (kg)	66 (2)	65 (3)	69 (2)	0.052
Sex (F/M)	5/7	4/8	4/9	0.851
Operation time (min)	190.5 (39.4)	147.2 (49.2)	203.7 (101.4)	0.062
ASA	II-III	II-III	II-III	0.126

Table 3: Mean arterial pressures (MAP) values of groups

	Group 1	Group 2	Group 3	*P*-value
0 min	113 (7)	122 (6)	112 (10)	0.252
30th min	116 (6)	125 (5)	101 (8)□	0.025
60th min	104 (5)	111 (4)	96 (5)*	0.014
90th min	110 (4)	119 (3)	92 (7)□	0.021
120th min	109 (5)	109 (4)	102 (9)	0.070
3th hour	104 (4)	111 (3)	105 (5)	0.069
4th hour	114 (6)	125 (5)	106 (4)*	0.016
6th hour	112 (5)	118 (4)	115 (5)	0.244
12th hour	110 (4)	115 (3)	113 (6)	0.357
24th hour	119 (2)	120 (1)	121 (2)	0.701
48th hour	123 (2)	121 (2)	122 (2)	0.527

*: between groups 3 and the others, □: between groups 3 and 2

Table 4: Mean numeric rating scale (NRS) of pain scores of groups

	Group 1	Group 2	Group 3	*P*-value
0 min	5.1 (1.4)	4.2 (1.6)	3.2 (1.3)	0.062
30th min	4.5 (1.1)	5.2 (1.3)	2.0 (1.5)*	0.009
60th min	4.2 (1.3)	4.8 (1.5)	2.5 (1.3)*	0.012
90th min	3.3 (1.2)	4.2 (1.1)	2.0 (1.3)*	0.019
120th min	3.8 (1.4)	3.5 (1.3)	1.5 (1.2)*	0.034
3th hour	3.5 (1.3)	3.1 (1.2)	1.3 (1.2)*	0.021
4th hour	3.5 (1.2)	3.0 (1.3)	1.0 (1.3)*	0.038
6th hour	3.2 (1.3)	3.1 (1.1)	1.0 (1.3)*	0.023
12th hour	2.8 (1.2)	2.7 (1.4)	1.2 (1.4)*	0.041
24th hour	2.0 (1.2)	2.5 (1.2)	0.6 (1.1)*	0.031
48th hour	0.5 (1.3)	1.6 (1.2)	0.7 (1.0)	0.055

*: between groups 3 and the others

Discussion

A quality postoperative analgesia is one of most important goals of anesthesia. Despite all this interest,

postoperative analgesia is usually inadequate [1,2]. Earlier studies showed that epidural analgesia is more effective then intravenous or intramuscular opioids [11-13]. Epidural analgesia also has some more advantages. Early resolving of gastrointestinal function, lower postoperative pulmonary complications, lower myocardial ischemia incidence, better mobilization, lower thromboembolism risk and less chronic pain problems are some of these advantages.

Studies comparing patient controlled epidural analgesia with conventional epidural infusion or bolus techniques showed that, patient controlled epidural analgesia is a better analgesia therapy and a safer technique with higher patient satisfaction [14,15]. Liu et al. [16] reported in a study, better analgesia with less complications with patient controlled epidural analgesia then epidural infusion or epidural bolus analgesia techniques, conducted on 454 abdominal, 165 gynecological, 126 urologic, 108 vascular, 90 thoracic, 83 orthopedic, and 4 plastic, total 1030 patients. Pruritus 12-28%, nausea 6-32%, hypotension 3-8%, sedation 9-24%, motor blockage 4-12%, respiratory depression 0.2-1.9% were found. There weren't any hematoma or abscess in the patients [16]. In our study, we found an adequate analgesia with no serious complications. We didn't see any pruritus, sedation or respiratory depression since we didn't use epidural opioids. We recorded nausea in one patient from group 1 and one patient from group 3 and successfully treated with metoclopramide.

We didn't see any serious hypotension since we gave enough intravenous fluid replacement before epidural catheterization and during epidural analgesia treatment. Blood pressure levels, in the third group at postoperative 60^{th} minute and 4^{th} hour were lower than the first and the second group. Blood pressure levels, in the third group at postoperative 30^{th} and 90^{th} minutes were lower than the second group. Since these blood pressure levels were within the physiological range, they didn't need any intervention. In the third group, patients were hypotensive despite enough fluid replacement during surgery, so we reduced dosage of the volatile anesthetic. Low dose of volatile anesthetics were used for anesthesia maintenance without any signs of awakeness. Intraoperative regional local anesthetics can adjunct to general anesthesia and lower the dosage of volatile anesthetics. Since our study protocol did not involve volatile anesthetic consumption, this effect needs to be studied in another study.

At the early postoperative period, for two hours, inhaler oxygen therapy via mask was given to one patient from group 1 and to two patients from group 2, because their SpO_2 levels were below 90%. These patients' operation types and sedation scores were not different from the average of their groups. These patients' NRS scores were 5, so they were in pain. Also these patients' intraoperative alfentanil consumptions were above the average. We assumed that these patients were not breathing easily because either they were in pain or they had respiratory depression because of high dose of alfentanil. After additional analgesic therapy and a complete recovery from anesthesia, SpO_2 levels were better and inhaler oxygen therapy was no longer needed.

Maximum plasma concentration of bupivacaine, rarely reaches toxic levels. Bupivacaine is an optimal agent for epidural infusion, because it has long duration of action with less motor blockage. Recurrent partial motor blockage was seen in one patient from group 1 and one patient from group 2. So epidural infusions of these patients' were terminated and excluded from the study. Motor blockage ratio was found 16% and exclusion ratio from the study for this reason was found 5.5% in this study. These ratios are compatible with previous studies [16,17]. Quinn Hogan [18] tried to explain the reason of partial motor blockage in a study which was conducted on 20 female patients. He studied distribution of contrast agent with CT, which was given through epidural catheter. He showed that contrast agent distributed asymmetrically and asymmetrically distribution increased as the given contrast agent increased. He argued that this asymmetric distribution is why, asymmetric blockage develops.

Many animal studies reported that preemptive analgesia helps postoperative analgesia management. Preemptive analgesia conducted on animals, with regional local anesthetics and intrathecal opioids was found effective [5,6]. But clinical studies are contradictory. Cho et al. [9] studied 60 patients who had subtotal gastrectomy. They found that epidural morphine and ketamine given before anesthesia induction was more effective then given at the end of surgery. Nakamura et al. [19] studied on 90 abdominal hysterectomy patients. They showed that epidural local anesthetics suppress central sensitivity providing lower pain scores at the postoperative period. But Dahl et al. [20] reported that there wasn't any difference with epidural bupivakain and morphine applied 40 minutes before surgery, in a study, conducted on 32 patients who had major abdominal surgery. Again Rice et al. [10] reported in a study conducted on 40 children ageing 18 months to 11 years old that, caudal block with bupivacaine either applied preoperatively or postoperatively does not affect postoperative analgesia.

Lack of existence of any difference between application of preoperative or postoperative analgesics in some clinical studies, is not a reliable evidence that, preemptive analgesia does not exist. It must be emphasized that, central hyperexcitability must be prevented, to achieve preemptive effect. The high intense of stimulation seen in major surgery is not only because of surgical incision but also because of some chemicals released from injured tissue [21]. For this reason, preemptive analgesia must also prevent central sensitization by chemicals released from injured tissue.

We couldn't find any difference between preoperative bolus group (group 2) and postoperative group (group1) on postoperative analgesia. In the postoperative infusion group after preoperative bolus and intraoperative infusion of bupivacaine (group 3), postoperative pain scores were lower than the other groups. The reason why, there was no difference between preoperative bolus and postoperative infusion group was probably that, the surgery time was longer then the duration of action of preoperatively administered bupivacaine or preoperative bolus bupivacaine was insufficient to suppress central hyperexcitability. But in the third group, since intraoperative infusion was given after preoperative bolus, central hyperexcitability have been prevented and also duration of action was not an issue. And lower pain scores were achieved in this group. Dahl et al. [20] and Rice et al. [10] probably

couldn't find any preemptive effect because they couldn't be able to suppress central sensitization with one bolus dose given preoperatively.

In the third group, intraoperative alfentanil consumption was lower than the other groups because intraoperative bupivacaine infusion is an effective way to suppress pain, during surgery.

Effective pain management can be achieved with the suppression of transduction, transmission, modulation and perception of pain with multimodal approach.

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Contribution of adapted physical activity on body composition and fitness related to the health of vascular hemiplegic patients

Vasküler hemiplejik hastaların sağlığı ile ilgili uyarlanmış fiziksel aktivitenin vücut kompozisyonu ve fitnesine katkısı

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Abstract

Aim: Stroke is a neurological deficit of vascular origin lasting more than 24 hours. We aimed to examine the impact of the functional rehabilitation associated with the practice of adapted physical activities on body composition and fitness related to the health of vascular hemiplegic patients.

Methods: We chose the case-control study method which is consisted to evaluate the body composition and health-related fitness of 90 male hemiplegic patients, after randomization, 40 of whom were in the experimental group undergoing a functional rehabilitation program associated with the practice of adapted physical activities and 50 of the control group submitted to a functional rehabilitation program.

Results: After the two intervention programs we found that subjects in the experimental group significantly changed total fat, visceral fat and muscle compared to the control group (P<0.001, P=0.004 and P=0.029, respectively). Their resting heart rate, respiratory rate, muscle strength, walking speed and rate were significantly reduced compared to the control group (P<0.001 for all mentioned comparisons). In addition, their resting systolic blood pressure, resting diastolic blood pressure, forced expiratory volume, muscle strength and Motor skills were significantly improved compared to the control group (P=0.048, P=0.027, P=0.003, P=0.015 and P=0.003, respectively).

Conclusion: This study shows that the functional rehabilitation program associated with the regular practice of adapted physical activities is more beneficial in improving the morphological state and fitness of hemiplegic patients than the isolated use of functional rehabilitation.

Keywords: Adapted physical activity, Fitness, Hemiplegia

Öz

Amaç: İnme, 24 saatten fazla süren, vasküler orijinli bir nörolojik eksikliktir. Uyarlanmış fiziksel aktivitelerle ilişkili fonksiyonel rehabilitasyonun, vücut kompozisyonu ve vasküler hemiplejik hastaların sağlığı ile ilgili uygunluk üzerindeki etkisini incelemeyi amaçladık.

Yöntemler: 90 erkek hemiplejik hastanın vücut kompozisyonu ve sağlıkla ilgili uygunluğunu değerlendirmek için oluşturulan olgu-kontrol çalışma yöntemini seçtik, randomizasyondan sonra 40'ının uygulamalı fonksiyonel rehabilitasyon programına aldık. Fonksiyonel rehabilitasyon programına sunulan fiziksel aktiviteler ve kontrol grubunun 50'sine uyarlandı.

Bulgular: İki müdahale programından sonra, deney grubundaki deneklerin toplam yağ, visseral yağ ve kası kontrol grubuna anlamlı olarak değiştirdiğini bulduk (Sırasıyla P<0.001, P=0.004 ve P=0.029). Dinlenme kalp hızı, solunum hızı, kas kuvveti, yürüme hızı ve hızı kontrol grubuna göre anlamlı olarak azaldı (belirtilen tüm karşılaştırmalar için P<0.001). Ayrıca istirahat sistolik kan basıncı, istirahat diyastolik kan basıncı, zorlu ekspiratuvar volümü, kas kuvveti ve Motor becerileri kontrol grubuna göre anlamlı olarak düzeldi (Sırasıyla, P=0.048, P=0.027, P=0.003, P=0.015 ve P=0.003).

Sonuç: Bu çalışma, uyarlanmış fiziksel aktivitelerin düzenli olarak uygulanmasıyla ilişkili fonksiyonel rehabilitasyon programının, hemiplejik hastaların morfolojik durumlarını ve fiziksel durumlarını iyileştirmede, fonksiyonel rehabilitasyonun izole kullanımına göre daha faydalı olduğunu göstermektedir.

Anahtar kelimeler: Uyarlanmış fiziksel aktivite, Fitness, Hemipleji

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Introduction

Stroke is the second leading cause of death in the world and in developing countries (developing countries), behind cardiovascular diseases, infectious diseases, especially pulmonary or diarrheal infections, tuberculosis, aids or malaria [1]. The risk of stroke doubles for each successive decade after the age of 55 and between 55 and 75 years. The incidence is 50% higher in men than in women, and the risk of recurrent vascular events is high and may vary according to stroke pathophysiology, comorbidities, and lifestyle risk factors [2-6]. Although most of the stroke is not life-threatening in the first case, the majority of people who have died from a disability accident or new vascular events [7].

There are several risk factors for stroke: high blood pressure, tobacco overuse of salt and alcohol, overweight, diabetes mellitus, bleeding disorders, hypercholesterolemia and physical inactivity [8].Recent studies have shown that individuals after stroke have not only a residual motor and cognitive impairment but also a low ability to withstand physical exertion, where about 70% of them show a coexisting type of heart. In addition to this, the energy that these individuals spend to perform their activities of daily living is significantly higher than in people without functional impairment [9,10]. Although this poor ability to perform physical exertion can be attributed to the regular aging process, studies have shown that aerobic fitness in these individuals is about 40% lower than in sedentary individuals of the same sex and age; which may contribute to increased risk of future stroke or acute myocardial disease [11].

The benefits of regular physical activity provide better control of high blood pressure and hyperlipidemia. Blood viscosity and platelet aggregation are reduced, decreasing the risk of thrombosis [12]. The blood vasodilatation produced during an effort causes the patients a decrease in blood pressure and promotes a good heart condition [13]. Following an effective solicitation of different metabolic systems (respiratory, muscular ...), cardiac adaptation at rest and exercise is better and blood pressure is reduced for the same activity [14].

For muscular and ventilatory functions, bed rest and activity restriction after stroke lead to muscle wasting and exercise deconditioning [15]. Thanks to the mechanical constraints, the physical activity increases the mass and the muscular force without modifying the spasticity [16]. Functional abilities such as stamina and walking speed are improved, as is exercise tolerance. The effects of regular physical activity on the ventilatory function stimulate the alveolar exchanges allowing a better oxygenation of the muscles [17].

However, in the Democratic Republic of Congo (DRC), the re-educational care begins to associate more and more the practice of physical activity but we found that no study was conducted to evaluate the effects of this activity on fitness parameters including muscle strength, stamina and walking speed etc. That's what motivated us to conduct this study.

Materials and methods

Nature, period and framework of study

We opted for the case-control study method that assessed the health status of hemiplegic patients over a 4 month period from September 2018 to January 2019.

The present study was conducted at University Clinics of Kinshasa and the Kinshasa Reference General Hospital. The choice of these institutions is justified by the fact that they are institutions of reference in the Democratic Republic of Congo and that they receive many hemiplegic patients.

Population, sampling and sample

This study consisted of 120 male hemiplegic patients attending the two hospitals mentioned above. In this study we used the random sampling. Of 120 hemiplegic patients approached, 15 were excluded for various reasons.

Of the total reduced to 105 hemiplegic patients, there were 15 additional exclusions during study for voluntary discontinuation (n=6), health problem (n=4), lack of time (n=3); 2 hemiplegic patients were lost sight of. The final experiment thus covered 90 subjects.

Our sample consisted of 90 male hemiplegic patients, 40 of whom were subjected to a rehabilitation program associated with the practice of adapted physical activities (experimental group) and 50 hemiplegic patients subjected only to a rehabilitation program (control group).

The local ethics committee of Physical Medicine and Rehabilitation Department, University Clinics of Kinshasa approved the study that was prepared according to ethical standards of 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000.

The following inclusion criteria were applied (Figure 1):

- To be a hemiplegic patient;
- To follow the sessions in two institutions selected for our study;
- Do not present a contraindication to the practice of physical activity;
- Have participated in at least 95% of sessions;
- Be present on the first and last day of assessment;
- To freely accept to participate in this study.
- All hemiplegic subjects who did not meet the exclusion criteria mentioned above were excluded.

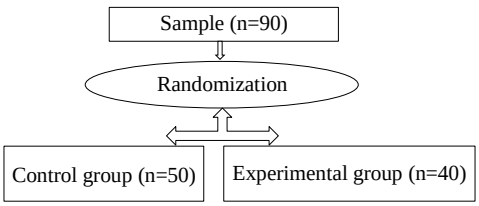

Figure 1: Group repartition

Data gathering

Anthropometric measurements

To keep as much discretion as possible, the anthropometric measurements were taken away from the rest of the group.

These measures include body weight, height, body mass index (BMI) and body fat percentage of participants. In order to determine the percentage of body fat of the participants, the skin folds (triceps, biceps, subscapularis and supra ailiac) will be measured using a vernier caliper [18] located on the right side of the body. The percentage of body fat was calculated according to Oja and Tuxworth (1995).

- Body weight (kg): The weight of the barefoot participant was measured with bioimpedance weighing (Tanita TBF-300A) calibrated to only take body weight, with an accuracy of 0.1 kg.
- Body size (m): The size was measured with inspiration stuck with a barefoot participant. The device used is a Seca 214 portable stadiometer with a 1 mm scale attached to a wall. The subject is positioned on the stadiometer with contact at the heels, buttocks, shoulder blades and (if possible) the skull. The subject's head is positioned according to the Frankfurt plane (i.e. the path from the highest point of the external auditory canal to the lowest point of the lower orbital rim is parallel to the ground) [19].
- Waist circumference (cm): Waist circumference will be measured using a single anatomical landmark, the upper lateral ridge of the iliac crest at the midaxillary line. The lower edge of the tape measure will be placed on the superior lateral ridge of the iliac crest at the midaxillary line [20].
- The body mass index (kg/m^2): The BMI was calculated directly by applying the formula in the database during interpretation. Subsequently, by applying the "WHO Reference 2007 SPSS macro package" [21] to the database, it was possible for us to obtain an estimate of the z-score of the referenced participant's BMI to the database. 2007 WHO BMI-for-age, by sex and age [21].
- Body composition (%): The body composition was evaluated using an Omeron BF-511 scale impedance meter; it was used to evaluate the percentage of total fat (TF), percentage of visceral fat (VF) and percentage of muscle.

Measurement of physiological parameters

- The resting heart rate is measured using a stethoscope and blood pressure using a mechanical sphygmomanometer;
- Respiratory frequency (RF) (cycle/min): it was taken using a stopwatch;
- Forced expiratory volume (FEV) per second (%): It was evaluated using a Piko-6 brand spirometer

Motor evaluation

The Cardiorespiratory endurance, perception of the effort and walking performance parameters were assessed before and after the program. Functional capacity was measured by the six-minute walk test, which allowed us to calculate the maximum oxygen consumption using the formula: VO_2 max (ml/kg/min): 26.9 + 0.014 x dist TDM6 (m) -0.38x BMI (kg/m^2 ; the walking speed was measured with a stopwatch, the hemiplegic patients are timed while walking a distance of 6 m at their preferred speed or spontaneous speed, the normal walking speed in the hemiplegic varies between 1.1 and 1.5 m/sec; the rate was measured as the number of steps per minute, the baseline was based on the size of the hemiplegic and ranged from about 90 steps / minute for tall subjects (1.83 m) to about 125 steps/minute for small subjects (1.5 m); Timed get up and go Test was evaluated thanks to the time taken by the subject to get up from a chair, walk 3 meters, turn around, go back to the seat and sit down; Strength and muscle power of the lower limbs was measured using the number of sit-stand achieved by the subject in 30 seconds, An impossibility or low score below five sit stand passages sign a level of dependence high.

Exercise protocol

For the control group

To best guide the work of the therapists and help them in setting up the collective, 90 cards have been developed. They are intended for patients and follow three exercise models: stretching and functional movement. Each card illustrates an exercise concerning the upper limb, the lower limb or the trunk and is accompanied by an explanatory text. They want to be clear and understandable for the patients, bringing to the therapists situations of exercises that are easy to put in place.

For the experimental group

In addition to the rehabilitation program offered to the control group, a program of physical exercises consisting of treadmill exercise, exercises on ergo manual cycle, balance (static and dynamic), flexibility exercises and muscle strengthening of abdominals, members Upper and lower was added for the experimental group. These exercises were performed twice a week with duration of 45 minutes at a moderate intensity. The cardio frequency meter allowed us to monitor the intensity of the exercise.

Statistical analysis

Quantitative variables are presented as mean (standard deviation). Comparisons between control and experimental groups are made by a student t test (SPSS software). A threshold of significance at $P<0.05$ is retained.

Results

Table 1 shows that before the intervention program, no significant difference was observed between the experimental group and the control group. After the program we found that the experimental group had significantly reduced their percentage of total and visceral fat, but their percentage of muscle increased.

Table 2 shows that before the program, the experimental and control groups showed no statistically significant difference. After the intervention program, we observed that subjects in the experimental group compared to the control group significantly improved their physiological and physical fitness parameters.

Table 1: Comparison of mean values of sociodemographic parameters and body composition before and after the intervention program

	Before the program			After the program		
	EG	Control		EG	Control	
Parameters	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	Mean (SD)	*P*-value
Age (years)	53(6.2)	51(5.7)	0.061	53(6.2)	51(5.7)	0.061
Heigh(cm)	173.1 (10.5)	171.4 (8.1)	0.272	173.1 (10.5)	171.4 (8.1)	0.272
Weight (kg)	82.6 (4.7)	83.1 (9.03)	0.078	80.1 (6.03)	82.2 (12.86)	0.084
BMI (kg/m²)	28.28 (1.3)	28.46 (0.5)	0.092	26.78 (0.61)	28.15 (6.22)	0.061
TF (%)	32.1 (1.6)	33.7 (1.9)	0.073	27.03 (1.4)	32.7 (5.12)	<0.001*
VF (%)	24.3 (0.71)	22.01 (1.1)	0.064	20.1 (1.08)	23.39 (8.1)	0.004*
Muscle (%)	11.2 (3.6)	12.01 (2.2)	0.089	18.52 (1.33)	11.4 (5.2)	0.029*

EG: Experimental group, TF: Total fat, VF: Visceral fat, * Student's t-test: significant, BMI: Body mass index

Table 2: Comparison of mean values of physiological parameters and physical condition before and after the intervention program

	Before the program			After the program		
	EG	Control		EG	Control	
Parameters	Mean (SD)	Mean (SD)	*P*-value	Mean (SD)	Mean (SD)	*P*-value
Heart rate (beat/min)	80.5 (5.2)	82.7 (10.06)	0.061	78.9 (3.22)	81.7 (9.73)	<0.001*
resting systolic blood pressure (mmHg)	135.1 (9.03)	134.3 (8.17)	0.073	129.3 (6.03)	134.3 (8.17)	0.048*
resting diastolic blood pressure (mmHg)	86.6 (7.16)	87.41 (6.92)	0.081	82.3 (5.21)	86.33 (4.02)	0.027*
Respiratory frequency (cycle/min)	25.35 (1.91)	26.5 (2.62)	0.062	20.12 (1.76)	25.4 (1.81)	<0.001*
Forced expiratory volume (%)	62.71 (10.3)	61.51 (7.12)	0.083	68.95 (6.04)	61.51 (7.12)	0.003*
muscle strength (new)	20.6 (1.82)	22.03 (1.54)	0.099	24.2 (1.31)	22.03 (1.54)	0.015*
Walking speed (m/sec)	0.62 (0.03)	0.64 (0.02)	0.078	0.42 (0.01)	0.62 (0.08)	<0.001*
Risk of falling	17.04 (1.8)	17.51 (1.06)	0.287	26.09 (1.5)	16.34 (1.92)	<0.001*
Motor skills(sec)	31.3 (5.06)	32.43 (7.41)	0.091	25.01 (1.44)	31.71 (2.71)	0.003*
Rate (pas/min)	30.28 (7.08)	31.05 (9.18)	0.793	37.63 (1.56)	29.22 (3.94)	<0.001*
Endurance cardiorespiratory (ml/kg/min)	19.41 (1.99)	17.49 (1.52)	0.062	25.55 (1.08)	18.41 (1.03)	<0.001*

EG: experimental group, * Student's t-test: significant

Discussion

The objective of this study was to evaluate the influence of the practice of adapted physical activities associated with reeducation sessions. This study showed that patients in the experimental group significantly changed their body composition compared to the control group.

Our results corroborate those of Bofosa et al [22] who demonstrated that regular exercise can change the body composition of practitioners.

Training aerobic capacity after stroke improves walking and physical stamina, decreases lower heart rate, improves self-perception and general well-being [23]. When strength and aerobic workouts are combined, there is a significant improvement in maximum oxygen uptake, increased muscle strength and weight loss [23]. Stretching and flexibility exercises can help maintain joint mobility, while balance and proprioception exercises can help prevent falls [24]. In our study, we observed the same thing as the previous findings. Subjects in the experimental group after the practice of adapted physical activities significantly improved their cardiorespiratory endurance, heart rate, and grip strength compared to the control group. Adapted physical activity prevents falls, maintains bone density and makes it easier for stroke patients to carry out activities of daily living [25]. This literature corroborates the results of our study, which show that patients in the experimental group compared to the control group significantly reduced their risk of falling.

The benefits of regular physical activity provide better control of arterial hypertension and hyperlipidemia [26]. Blood viscosity and platelet aggregation are reduced, decreasing the risk of thrombosis. The blood vasodilatation produced during an effort causes the patients a decrease in blood pressure and promotes a good heart condition [27]. Following an effective solicitation of different metabolic systems (respiratory, muscular ...), cardiac adaptation to rest and exercise is better and blood pressure is reduced for the same activity [28]. In our study, blood pressure was also evaluated. We observed that patients in the experimental group significantly reduced their blood pressure compared to the control group. This could be justified by the fact that the low level of adapted physical activities is corroborated with the risk of presenting arterial hypertension.

For muscular and bladder functions, bed rest and restriction of activity after AVC lead to muscle wasting and deconditioning on exercise [29]. Due to mechanical constraints, physical activity increases muscle mass and strength without altering spasticity [30]. Functional abilities such as endurance and walking speed are improved, as is exercise tolerance [31]. The effects of regular physical activity on the ventilatory function stimulate the alveolar exchanges allowing a better oxygenation of the muscles [32]. These findings from the literature corroborate those of our study, which shows that experimental group subjects increased their walking speed, a number of steps, and this in a statistically significant way.

This study is limited to the use of a small sample of a metropolitan city of the Democratic Republic of Congo, which will probably reduce the possibility of generalization of the results. Therefore, a future study of a more representative sample of hemiplegic patients is needed to potentially increase the generalizability in the country.

Conclusion

This study has shown that regular practice of adapted physical activities allows hemiplegic patients to improve their physiological parameters and physical condition. We suggest that this practice be internal in the hospital environment of Kinshasa.

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Biochemical and histopathological evaluation of taxifolin: An experimental study in a rat model of liver ischemia reperfusion injury

Taxifolinin biyokimyasal ve histopatolojik değerlendirilmesi: Rat modelinde karaciğer iskemi reperfüzyon hasarı üzerine deneysel çalışma

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Abstract

Aim: Ischemia/reperfusion (I/R) procedure applied during liver resection and transplantation in clinic settings causes liver oxidative damage. The aim of this study was to examine the effects of taxifolin on liver injury induced by I/R in rats.

Methods: Albino Wistar male rats divided into three groups with 6 rats in each group: liver ischemia-reperfusion (LIR), 50 mg/kg taxifolin + liver ischemia reperfusion (TLIR) and sham operation (SHAM). An hour before thiopental sodium anesthesia, 50 mg/kg taxifolin was orally administered to the TLIR group and distilled water to the LIR and SHAM groups. In the TLIR and LIR groups, a clamp was placed in the hepatic artery, portal vein and bile duct, thereby inducing ischemia for one hour, and reperfusion for six hours. In the SHAM group, the abdominal cavity was closed by surgical suture without any procedure. At the end of this period, rats were sacrificed with high dose anesthesia. Liver tissues were removed for biochemical and histopathological examinations

Results: I/R procedure significantly increased MDA (P<0.001), ALT, AST levels (P<0.001) and decreased tGSH level (P<0.001) in liver tissue compared to SHAM group. In the taxifolin treated group, this effect was suppressed. Histopathologically, in the I/R induced group, pathological findings such as dilated congested blood vessel, hemorrhage, destruction in the liver parenchyma and edema observed. Liver tissue in the taxifolin group had near-normal appearance except mild sinusoidal congestion.

Conclusion: Our results indicate that taxifolin is an effective agent in reducing hepatic damage caused by I/R.

Keywords: Ischemia, Reperfusion, Rat, Taxifolin

Öz

Amaç: Karaciğer rezeksiyonu ve transplantasyon sırasında uygulanan iskemi reperfüzyon (I/R) prosedürü karaciğerde oksidatif hasara yol açmaktadır. Bu çalışmanın amacı ratlarda iskemi reperfüzyonun neden olduğu karaciğer hasarına taxifolinin etkisini incelemektir. Yöntemler: Albino Wistar erkek ratlar her grupta 6 rat olmak üzere üç gruba ayrıldı: karaciğer iskemi reperfüzyon (LIR), 50 mg/kg taxifolin + karaciğer iskemi reperfüzyon hasarı (TLIR) ve sham operasyon (SHAM). Thiopental sodium anestezisinden bir saat önce TLIR grubuna 50 mg/kg taxifolin; LIR ve SHAM grubuna ise distile su uygulandı. TLIR ve LIR gruplarında hepatik arter, portal ven ve safra kanalına bir saat iskemi ve altı saat reperfüzyon oluşturmak üzere klemp yerleştirildi. SHAM grubunda herhangi bir prosedür uygulanmadan karın boşluğu cerrahi dikişle kapatıldı. Bu periyodun sonunda ratlar yüksek doz anestezi ile sakrifiye edildi. Karaciğer dokuları biyokimyasal ve histopatolojik inceleme için çıkarıldı. I/R prosedüründe SHAM grubu ile kıyaslandığında karaciğer dokusunda MDA (P<0,001), AST, ALT (P<0,001) değerlerinde anlamlı artış ve tGSH (P<0,001) değerinde azalma görüldü. Taxifolin uygulanan grupta bu etki baskılandı.

Bulgular: I/R grubunda patolojik olarak dilate konjeste kan damarları, hemoraji, karaciğer parankiminde destrüksiyon ve ödem gözlendi. Taxifolin uygulanan grupta karaciğer dokusu orta derecede sinusoidal konjesyon dışında normale yakın görünümdeydi.

Sonuç: Sonuçlarımız taxifolinin iskemi reperfüzyon sonrası oluşan karaciğer hasarını önlemede etkili olduğunu göstermektedir.

Anahtar kelimeler: İskemi, Reperfüzyon, Rat, Taxifolin

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Introduction

Ischemia/reperfusion (I/R) applied during liver resection and transplantation in clinical settings causes liver damage in the postoperative period [1,2]. I/R is known to cause tissue damage. I/R damage include a number of complex pathophysiological conditions. Therefore, the pathogenesis of I/R injury has not been fully elucidated [3]. However, it is known that reperfusion of ischemic tissue paradoxically leads to more serious conditions than ischemia-related damage. [4]. In addition, high free oxygen radical (FOR) formation from the molecular oxygen presented in abundant amounts to the ischemic tissue by arterial blood is considered to be responsible for reperfusion injury [5]. Uncontrolled production of FORs cause oxidation of cell membrane lipids and proteins, cytokine production and tissue inflammation [6]. Unless it could be presented, it results in liver damage and failure [7]. Therefore, a large number of antioxidants and anti-inflammatory drugs are currently being tested against liver I/R damage [8,9].

Taxifolin (3,3′, 4′, 5,7-pentahydroxiflavanon) which has been examined in this study for its protective effect against liver I/R damage, is a flavanone found in onions, milk thistle, French maritime and Douglas fir bark [10]. The antioxidant and anti-inflammatory activity of taxifolin has been proven [11,12]. This information suggests that taxifolin may be effective and convenient in protecting liver I/R injury. So far there are no studies analyzing the effect of taxifolin on I/R induced liver injury in the literature. Therefore, the purpose of our examination was to analyze the effect of taxifolin on I/R induced liver injury in rats by biochemical and histopathological techniques.

Materials and methods

Animals

In the study 18 albino rats weighing 260-275 grams were used. The animals were kept and fed in groups at under appropriate conditions prior to the study. Animal experiments were done according to the National Guidelines for the Use and Care of Laboratory Animals and were confirmed (Ethics Committee Number: 75296309-050.01.04-E.1800138985, Dated: 04.05.2018)

Chemicals

In the study thiopental sodium was provided from İ.E ULAGAY (Turkey), and taxifolin was provided from Evalar-Russia.

Animal Groups

Rats were separated into three groups: Liver ischemia reperfusion (LIR), 50 mg/kg taxifolin + Liver ischemia reperfusion (TLIR) and sham operation (SHAM).

Experimental Procedure

Anesthesia

Surgical operations were done under anesthesia by injecting thiopental sodium and xylazine to peritoneum at proper intervals under sterile circumstances. After thiopental sodium injected to the rats, and waited for appropriate surgical time. The moment when the animals were immobilized in the supine position was considered as the appropriate time of anesthesia for surgical examination [8].

Surgical and pharmacological procedures

One hour prior to thiopental sodium anesthesia, the animals in the TLIR group (n-6) were orally given a 50 mg/kg dose of taxifolin. LIR and SHAM groups were treated with distilled water as solvent with the same method. During anesthesia, all rats were placed in the supine position, in front of the abdomen was vertically cut (3.5-4 cm long), and laparotomy was performed. In the SHAM group, abdominal cavity was closed by surgical suture without any procedure. For increase total hepatic ischemia, a clamp was placed in the hepatic artery, portal vein, and bile duct for one hour in the TLIR and LIR groups to induce ischemia for one hour and reperfusion for six hours. At the end of this period, rats were sacrificed with high dose anesthesia. Liver tissues were removed for biochemical and histopathological examinations

Biochemical analyses

Malondialdehyde (MDA) analysis

MDA calculations were based on spectrophotometrical measurement of absorbance of the pink-colored complex formed by MDA and thiobarbituric acid (TBA). The mixture was twisted for a minute and centrifuged for ten minutes at 4000 rpm. The absorbation of the supernatant was measured at 532 nm. The standard curve was obtained by using 1,1,3,3-tetramethoxypropane [13].

Total Glutathione (tGSH) analysis

Glutathione analysis done according to the method defined by Sedlak J [14].

Alanine Aminotransferase (ALT) and Aspartat Aminotransferase (AST) analyses

Serum ALT and AST activities were calculated spectrophotometrically for the liver function tests.

Statistical analysis

All data analyzed using SPSS program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The results expressed as mean (standard deviation). The differences between groups were obtained using one-way ANOVA test then, Bonferroni test performed as posthoc. Significance level declared at $P<0.05$.

Results

Biochemical results

As shown in Figure 1, the I/R procedure significantly increased MDA level in liver tissue compared to the SHAM group and decreased tGSH level. Taxifolin administration decreased MDA level compared to the I/R group and the difference between the SHAM group and taxifolin group was not statistically significant. The decrease in tGSH level was suppressed by taxifolin administration and the difference between the I/R group and the taxifolin group was significant (Figure 1).

I/R procedure applied to liver significantly increased serum ALT and AST levels compared to the SHAM group. Taxifolin medication decreased these elevated levels in the I/R group and brought ALT and AST levels to those of the level of SHAM group. The difference between the taxifolin group and the SHAM group was not statistically significant ($P=0.02$) (Figure 2).

Histopathological results

As shown in Figure 3A, the liver tissue of the SHAM group had normal portal region, central vein and liver cell cords. However, I/R treated LIR group showed pathological findings such as dilated congested blood vessel, hemorrhage, destruction in the liver parenchyma and edema in the liver tissue (Figure 3B). In addition, dilated congested sinusoids were detected in the liver (Figure 3C). The TLIR group treated with taxifolin had liver tissue with near-normal appearance except for persistent mild sinusoidal congestion (Figure 3).

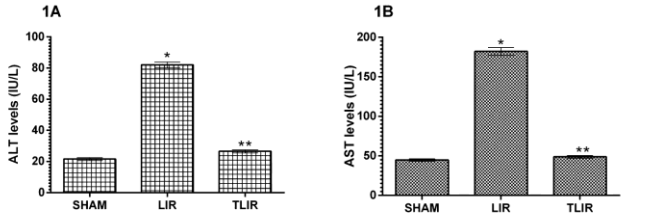

Figure 1: Levels of oxidant antioxidant parameters; 1A: MDA, 1B: tGSH. * *P*<0.001 according to SHAM group, ** *P*<0.001 according to LIR group. MDA- Malondialdehyde, tGSH- Total Glutathione, LIR- Liver ischemia-reperfusion, TLIR-50 mg/kg taxifolin + liver ischemia reperfusion, SHAM- sham operation

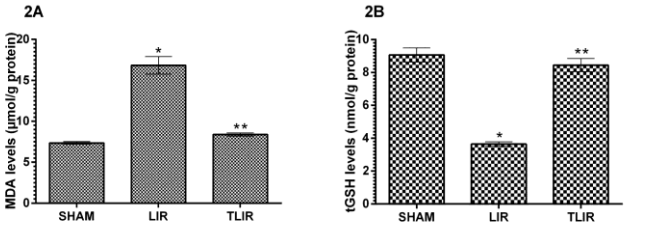

Figure 2: Levels of liver function tests; 2A: ALT, 2B: AST. * *P*<0.001 according to SHAM group, ** *P*<0.001 according to LIR group. ALT- Alanine aminotransferase, AST- Aspartate Aminotransferase, LIR- Liver ischemia-reperfusion, TLIR-50 mg/kg taxifolin + liver ischemia reperfusion, SHAM- sham operation

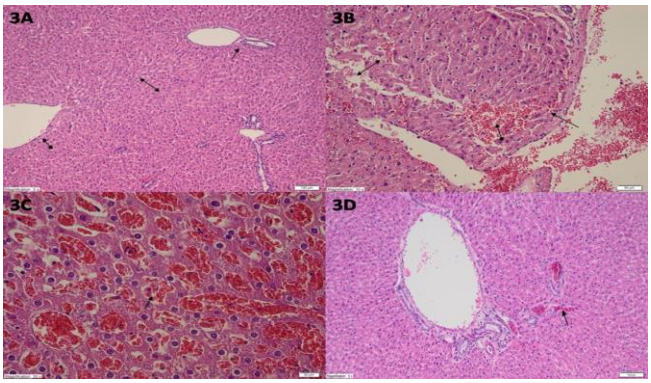

Figure 3: Histopathologic appearence of the liver tissues of experimental groups; 3A: In the liver tissue of SHAM group, normal portal area (straight arrow) , central vein (round arrow), and hepatic cell cords (double arrow) (HEX200), 3B: In the LIR group dilated congested blood vessels (straight arrow), hemorrhage (round arrow), liver parenchymal destruction and edema (double-sided arrow) (HEX100), 3C: Dilated congested sinusoids (arrow) in liver tissue of the LIR group (HEX400), 3D: In the TLIR group, normal portal area (straight arrow), central vein (round arrow), hepatic cell cords (double arrow) are observed (HEX200). LIR- Liver ischemia-reperfusion, TLIR-50 mg/kg taxifolin + liver ischemia reperfusion, SHAM- sham operation

Discussion

In present study, the effects of taxifolin on I/R induced liver injury in rats were examined biochemically and histopathologically. Our biochemical results revealed that the measure of MDA in liver tissue of animals medicated with I/R showed a significant increase compared to SHAM and taxifolin groups. Elevated levels of MDA in tissue are associated to increased free oxygen radicals in the tissue. The increase in free oxygen radicals (FOR) leads to an increase in lipid peroxidation. MDA is one of the final products of lipid peroxidation [15]. By causing cross-linking and polymerization of membrane components, MDA can inactivate membrane receptors and membrane-bound enzymes, resulting in serious damage to membrane proteins [16,17]. Demiryilmaz et al. [18] reported that I/R procedure caused oxidative damage in liver tissue by elevating MDA levels. Many studies show that MDA is an important parameter in evaluating liver oxidative damage [8,17-19]. As is known, MDA is noted as a marker that reflects oxidative stress in liver I/R injury and I/R injury of different organs [20,21]. In addition, MDA is known to be an efficient parameter in determining the seriousness of damage [20,22]. This information indicates that I/R procedure we induced in liver tissue increases the production of FOR and lipid peroxidation chain reaction occurs. In this regard, our findings are consistent with the literature.

As is known, antioxidants are produced in a continuous and controlled manner in living tissues against FORs. To maintain tissue integrity and function at normal levels, over-produced FORs are neutralized by endogenous glutathione GSH and other enzymatic and non-enzymatic antioxidants. If the antioxidants are insufficient to neutralize the oxidants, the oxidant/antioxidant balanced is disrupted towards the oxidants [23,24]. GSH reacts with the hydrogen peroxide (H_2O_2) involved in FOR formation to detoxify H_2O_2 and thus protects cells from FOR damage [25]. The results of our experiments, which are consistent with the literature, showed that the amount of tGSH decreased significantly in the liver tissue treated with I/R. This result shows that the balance between oxidants and antioxidants was disrupted in the I/R group in favor of the oxidants. Different studies also show that I/R and toxic substances decrease the amount of tGSH in liver tissue [8,26].

In this study, it has been noted that ALT and AST activities in the I/R group with increased MDA levels and decreased tGSH levels were meaningfully higher compared to the other groups. ALT and AST values are used to determine liver toxicity [27]. Recently, ALT and AST have been used more frequently in evaluating liver I/R injury [28]. The increase in ALT and AST activities is due to an over-increase in hepatocellular necrosis or cell membrane permeability [29]. Previous studies indicate that ALT and ASTs are directly related to the increase in oxidant parameters [8].

In our study, it was revealed that MDA and tGSH levels in the taxifolin group used against liver I/R damage were very close to the SHAM group. This shows that taxifolin prevents the disruption of oxidant-antioxidant balance in advantage of oxidants in I/R-administered liver tissue. Akinmoladun et al. [30] also stated that taxifolin showed antioxidant activity and protected liver tissue from FOR-related oxidative stress. They also reported that taxifolin inhibited MDA and H_2O_2 increase and tGSH decrease.

Our histopathological findings also support our biochemical results. Liver tissue of LIR group with increased MDA, ALT and AST levels and decreased tGSH levels showed pathological findings such as significantly dilated congested blood vessels, hemorrhage, parenchymal destruction, dilated congested sinusoids and edema. However, only mild sinusoidal congestion was monitored in the taxifolin-treated liver tissue of the TLIR group.

In the previous study, I/R was found to cause pathological damage like necrosis, hemorrhage, edema, leukocyte infiltration and dilated congested blood vessels in the gastric mucosa [31]. The disappearance of pathological findings

in the taxifolin group may be due to its antioxidant activity. Antioxidant activity has been shown to be important in reducing I/R damage [31,32].

Biochemical results showed that I/R procedure caused oxidative stress in the liver, and this was supported by histopathological findings. We found that taxifolin protects liver tissue from oxidative I/R damage. Our results indicate that taxifolin is an effective agent in reducing hepatic injury caused by I/R.

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Effects of the stone density on the outcome of percutaneous nephrolithotomy in pediatric population

Pediatrik popülasyonda taş dansitesinin perkütan nefrolitotomi sonuçlarına etkisi

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Abstract

Aim: The measurement of the stone densities of urinary system calculi in Hounsfield units (HU) using non-contrast computed tomography (NCCT) provides information regarding the composition and hardness of the stones. This study aims to evaluate the effects of stone HU values on the percutaneous nephrolithotomy (PCNL) outcomes in pediatric stone disease patients.

Methods: In this retrospective cohort study, the records of 57 pediatric patients, who had undergone PCNL between 2010 January and 2018 May, were evaluated. Demographic data, stone characteristics, peroperative changes, outcomes, and complications were obtained from patient records. The patients were divided into two groups based on their HU values: the low HU group (HU ≤1000) and the high HU group (HU >1000).

Results: A total of 61 PCNL operations were performed on 57 pediatric patients. Overall median stone size was 420 mm^2 – 475 mm^2 (78-2475) and simple/complex stone rate was (52.4%) / 29 (47.5%). A total of 38 patients were examined using NCCT prior to the operation. Twenty-two of the patients had an HU value ≤1000, whereas 16 had an HU value>1000. There were no statistically significant differences between the low and the high HU groups in terms of the duration of procedure, fluoroscopy time, success rates, and complications.

Conclusion: PCNL surgery is an effective method for the treatment of large and complex stones in the pediatric population. We determined that in pediatric patients who were evaluated using NCCT prior to PCNL the stone HU values of did not influence PCNL success.

Keywords: Hounsfield unit, Kidney stone, Percutaneous nephrolithotomy, Pediatrics

Öz

Amaç: Kontrastsız bilgisayarlı tomografi (BT) kullanılarak, üriner sistem taşlarının Hounsfield ünitesi (HU) ölçümü ile, taşların dansiteleri hakkında bilgi verir. Bu çalışmada, pediatrik taş hastalığı olan hastalarda taş HU değerlerinin perkütan nefrolitotomi (PCNL) sonuçları üzerindeki etkileri değerlendirildi.

Yöntemler: Bu retrospektif kohort çalışmasında, Ocak 2010 ve Aralık 2018 tarihleri arasında PCNL uygulanan 61 pediatrik hastanın kayıtları değerlendirildi. Hasta kayıtlarından tüm hastaların demografik verileri, taş özellikleri, peroperatif değişiklikleri, sonuçları ve komplikasyonları tarandı. Operasyon öncesi BT çekilen çocuk hastaların taş yapıları, HU değerlerine göre iki gruba ayrıldı: düşük HU grubu (HU ≤1000) ve yüksek HU grubu (HU >1000).

Bulgular: 61 pediatrik hastaya toplam 65 PCNL operasyonu uygulandı. Tüm hastaların medyan taş boyutu 420 mm^2 – 475 mm^2 (78-2475), basit / kompleks taş oranı 36 (%55,3) / 29 (%44,6) idi. Operasyon öncesi BT kullanılan toplam 38 hasta incelendi. Hastaların 22'sinde HU değeri ≤1000 iken, 16'sında HU değeri >1000 idi. Düşük ve yüksek HU grupları karşılaştırıldığında, gruplar arasında işlem süresi, floroskopi zamanı, başarı oranları ve komplikasyon oranları açısından istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: Pediatrik popülasyonda uygulanan PCNL ameliyatı, büyük ve kompleks taşların tedavisi için etkili bir yöntemdir. PCNL'den önce BT kullanılarak değerlendirilen pediatrik hastalarda, taş HU değerlerinin PCNL başarısını etkilemediğini belirledik.

Anahtar kelimeler: Hounsfield ünit, Böbrek taşı, Perkutan nefrolitotomi, Pediatri

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Introduction

Stone disease is a significant health problem for the pediatric population, especially in countries such as Turkey, where the stone disease is endemic [1]. Due to high recurrence rates, minimally invasive treatments that offer high stone-free success rates such as shock-wave lithotripsy (SWL), retrograde intrarenal surgery (RIRS), and percutaneous nephrolithotomy (PCNL) have priority over open surgery in the treatment of stone disease in the pediatric patients [2]. In their guidelines on pediatric urology, the European Association of Urology recommends PCNL surgery as the primary treatment for pediatric staghorn stones, kidney pelvic stones larger than 2 cm, and lower pole kidney stones larger than 1 cm [3]. On the other hand, the risk of PCNL resulting in potential renal damage, potential complications such as hemorrhage, and the associated radiation exposure may cause concerns for both the surgical team and the parents. However, latest publications report that this surgery can be safely performed with high success and low complication rates even in pre-school children [4,5].

The measurement of the stone densities of urinary system calculi in Hounsfield units (HU) using non-contrast computed tomography (NCCT) provides information regarding the composition and hardness of the Stones [6]. Numerous studies investigating adult and pediatric patients have shown that there is a relationship between the stone density and SWL success. [7-10]. The effect of this value on the outcomes of RIRS and PCNL performed on adult patients has also been evaluate [11-13]. However, to the best of our knowledge, the direct effect of Stone density on the outcome of PCNL surgery performed on children has not been evaluated to date. In this study, we aimed to investigate the effects of HU values on surgical outcomes and complications by evaluating patients in various age groups, who had undergone PCNL surgery due to kidney stones and who had undergone preoperative NCCT examinations.

Materials and methods

Following the ethics committee's approval (Tepecik Training and Research Hospital, 2018/7-7, 06/28/2018) we retrospectively evaluated records of patients of ages 0-18, who had undergone PCNL operations at our urology clinic between the dates January 2010 and May 2018. We selected 57 pediatric patients. All patients were evaluated preoperatively with kidney ureter bladder (KUB) x-ray and ultrasound (USG) of the urinary system. Patients who had suspicious or inconclusive USG results, presented with kidney anomalies on urinary USG, had staghorn and semi-staghorn calculi, and had non-opaque stones, were examined with NCCT. Nineteen patients without indication for NCCT or who did not undergo NCCT were excluded from the study. Overall, 38 pediatric patients that had indications for and undergone NCCT were included in the study. The patients were divided into two groups based on their HU values: the low HU group (HU $\leq$ 1000) and the high HU group (HU > 1000). Moreover, patients were divided into three groups according to their age and comparisons of these age groups were also conducted. All patients were evaluated by pediatric and anesthesia teams. Demographic data, Stone characteristics, preoperative, peroperative, and postoperative changes, surgical outcomes, and complications were acquired from patient records. Full blood count, serum creatinine levels, bleeding profiles, complete urinalysis results, and urine cultures were evaluated preoperatively. Those who had sterile urine cultures were approved to surgery. Those who had resistant infections were started on antibiotherapy prior to and following the surgery. The NCCT with a 64 multislice CT device (Aquilion, Toshiba Medical Systems, Tokyo, Japan) was performed preoperatively on patients who had indications for NCCT. The region of interest (ROI) and the HU value were calculated automatically from the picture archiving and communication system (PACS). Stones were classified as opaque or non-opaque based on radiological data. Stone localization was determined as upper, middle, lower, lower calyx, and pelvis. Stone size was measured by multiplying the largest width and length of the stone. For patients who had multiple stones in their urinary system, stone size was calculated by measuring each stone and calculating the sum of individual stone sizes. In our study, the Stone was classified as non-complex if it had an isolated pelvic, upper calyceal, middle calyceal, or lower calyceal localization, and as complex if there were partial or complete staghorn calculi and if stones were localized in the renal pelvis with additional presence in any calyx. Hydronephrosis was classified according to the Society for Fetal Urology grading system as none-mild or moderate-severe [14].

Surgical technique: All PCNL operations were performed under general anesthesia. Prior to induction, patients were administered single-dose second-generation cephalosporin intravenously based on weight. First, in the lithotomy position, a 5F open-ended ureteral catheter was inserted to the ureter on the surgical side with cystoscopy and was affixed onto the Foley catheter. The patient was then placed in the prone position. The urinary system was accessed using an 18 Gauge Chiba (Boston Scientific, Natick, MA, USA) needle with the 'triangulation' or 'eye of the needle' technique along with fluoroscopy. Access location was recorded as below (infracostal) and above (supracostal) the 12th rib. Following access, a 0.038-inch hydrophilic guidewire (SensorTM Guide Wire, Boston Scientific, Natick, MA,USA) was advanced into the kidney. Stepwise or one-shot dilatation was performed with Amplatz dilators under the guidance of the sensor. PCNL procedures were performed using 20/24/30 Fr Amplatz sheaths (Amplatz sheat, Boston Scientific) and 17F rigid (Karl Storz) or 24F nephroscopes. Stone fragmentation was performed using an ultrasonic lithotriptor (Swiss LithoClast Master). At the end of the procedure, all patients had 14F nephrostomy catheters placed. Operative time (time period between the first kidney puncture and insertion of the nephrostomy tube) and fluoroscopy time were recorded. Foley catheters were removed on the 1st postoperative day. The nephrostomy catheter was removed on the 2nd postoperative day in patients who had clear urine and presented no complications. Postoperative complications were evaluated based on the modified Clavien grading system. 15 Complication rates associated with different age groups were also compared according to the Clavien grading system. Patients who manifested urine drainage in the nephrostomy tract for longer than 48 hours, had a double J stent inserted under general anesthesia. Stone-free states and residual fragments (>4mm)

were evaluated by using KUB x-ray performed on the 2nd postoperative day for opaque stones, and using urinary USG of the urinary system for non-opaque stones.

Statistical Method: For quantitative variables in the study, descriptive statistics were presented as mean (standard deviation) or median (min-max) based on assumptions, while the categorical data were presented as frequency (n) and percentages (%). If the parametric test assumptions regarding whether or not there is a difference between the HU <1000 and HU >1000 groups in terms of quantitative variables were satisfied, the Student's t-test was used, and if they were not satisfied, the Mann-Whitney U test was used. If the parametric test assumptions regarding whether or not there were any differences between age groups were not satisfied, the related analysis was performed using the Kruskal-Wallis test. For both the HU groups and the age groups, the effects of categorical variables on the groups were evaluated using the Pearson Chi-square Test, Fisher's Exact Test, or the Fisher-Freeman-Halton Exact Test based on the assumptions. For all tests, the probability of a Type I error was considered α=0.05.

Results

Our study evaluated 61 PCNL operations performed on 57 pediatric patients. Patients' age, gender, body mass index (BMI), stone characteristics, presence of previous SWL and stone surgery, hydronephrosis grades, peroperative-postoperative properties, and complication rates have been summarized in Table 1. Three patients who underwent PCNL had solitary kidneys and one patient had a double collecting system. Two patients had bilateral stones and underwent multiple PCNL operations in separate sessions. In addition, two other patients underwent a second PCNL session on the previously operated side, due to residual stones after the first session of PCNL. Comorbidities included thalassemia major in one patient and congenital visual impairment in another patient. NCCT scans were performed prior to the operation for a total of 38 patients who were to undergo PCNL. Twenty-two of the patients had an HU value ≤1000 (low HU group), whereas 16 had an HU value >1000 (high HU group). There were no statistically significant differences between the low and high HU groups in terms of age, stone size, duration of procedure, fluoroscopy time, success rates, individual incidences of grade 1, grade 2, grade 3, and grade 4 complications, and days of nephrostomy, and hospitalization (Table 2).

Patients were assigned to three groups based on age, group 1 (Ages 0-5), group 2 (Ages 6-12), and group 3 (Ages 13-18). The patients' characteristics, peroperative data, complication rates, and stone-free rates were compared with regard to their age groups (Table 3).

Table 1: Patient, stone characteristics and peroperative, postoperative outcomes

Parameter	Value
Patients, n	61
Renal units operated, n	65
Median age, years (min-max)	12 (2-18)
Mean (SD), years	11.5 (5.5)
Gender, n (%)	
Female	26 (42.6%)
Male	35 (57.3%)
Median BMI, kg/m2 (min-max)	18.54 (10.1-32.6)
Laterality: n (%)	
Right	28 (43%)
Left	37 (56.9%)
Median stone size, mm^2 (min-max)	420 (78-2475)
Mean (SD), mm2	680.1 (561.2)
Stone complexity, n (%)	
Simple	36 (55.3%)
Complex	29 (44.6%)
Stone opacity	
Opaque	62 (95.3%)
Nonopaque	3 (4.6%)
Previous stone interventions, n (%)	
None	48 (73.8%)
Ipsilateral SWL	8 (12.3%)
Ipsilateral PNL	5 (7.6%)
Ipsilateral open surgery	4 (6.1%)
Hydronephrosis degree, n (%)	
None-Mild	31 (47.6%)
Moderate-Severe	34 (52.3%)
Median operative time, mins. (min-max)	90 (24-155)
Mean (SD), mins	84.8 (29.5)
Median scope time, secs. (min-max)	120 (60-1220)
Mean (SD), secs	172.7 (172.2)
Sheath size, n (%)	
<22 Fr	31 (47.6%)
>22 Fr	34 (52.3%)
Accesses, n (%)	
Single	58 (89.2%)
Multiple	7 (10.7%)
Access number, Mean (SD)	1.1 (0.3)
Access, n (%)	
Infracostal	55 (84.6%)
Supracostal	10 (15.3%)
Hgb Preop-Postop, Mean (SD)	1.1 (1.1)
Hematocrit Preop-Postop, Mean (SD)	3.2 (3.2)
Median duration of nephrostomy, days (min-max)	2 (1-3)
Mean (SD), days	1.7 (0.5)
Median hospitalization days (min-max)	2 (1-10)
Mean (SD), days	2.7 (2.1)
Result, n (%)	
Stone-free	55 (84.6%)
Residual stone	10 (15.3 %)
Complications, n, (%)	
Grade 1	6 (9.2%)
Grade 2	5 (7.6%)
Grade 3	3 (4.6%)
Grade 4	0
Overall complication rates	14 (21.5%)

SD: Standard deviation, BMI: body mass index, Fr: French, SWL: shock-wave lithotripsy, PCNL: percutaneous nephrolithotomy, Hgb: Hemoglobin

Table 2: Comparison of the results according to HU groups

Characteristics	HU<1000 N=22	HU>1000 N=16	*P*-value
Age,			0.968[a]
Mean (SD), years	11.77 (5.8)	12 (4)	
Median age, years (min-max)	15 (3-18)	16 (4-18)	
Gender, n (%)			0.171[b]
Female	11 (50%)	5 (31.2%)	
Male	11 (50%)	11 (68.7%)	
Median stone size, mm^2 (min-max)	506 (238-2475)	412 (238-1760)	0.639[a]
Site of Stone location, n/%			0.832[b]
Simple	9 (40.9%)	6 (37.5%)	
Kompleks	13 (59.1%)	10 (62.5)	
Duration of the procedure, minutes Mean (SD)	89.09 (27.344)	95.133 (27.299)	0.518[c]
Median fluoroscopy time, seconds (min-max)	120 (75-600)	120 (60-380)	0.598[a]
Tract size, n (%)			0.832[b]
<22 Fr	9 (40.9%)	6 (37.5)	
>22 Fr	13 (59.1%)	10 (62.5%)	
Median days of nephrostomy (min-max)	2 (1-3)	2 (1-2)	0.987[a]
Median days of hospitalization (min-max)	1 (1-8)	2 (1-6)	0.065[a]
Success, n/%			0.871[b]
Stone Free	19 (86.3%)	13 (81.2%)	
Residual Stone	3 (13.6%)	3 (18.7%)	
Modified Clavien classification system, n/%			0.160[d]
Grade 0	19 (86.3%)	12 (75%)	
Grade 1	1 (4.5%)	2 (9.5%)	
Grade 2	1 (4.5%)	1 (4.8%)	
Grade 3	1 (4.5%)	1 (9.5%)	
Overall complication rates	3 (13.6%)	5 (25%)	

SD: Standard deviation, HU: Hounsfield Unit, Fr: French, [a] Mann-Whitney U Test, [b] Pearson Chi-square Test, [c] Student's t Test, [d] Fisher-Freeman-Halton Exact Test

Table 3: Comparison of the results according to groups

Total cases, n (%)	Group 1 n=13 (21.3%)	Group 2 n=17 (27.8%)	Group 3 n=31 (50.8%)	*P*-value
Age, years				-
Mean (SD)	3.8 (1)	8.8 (2)	16.6 (1.3)	
Median (min-max)	4 (2-5)	8 (6-12)	17 (13-18)	
Gender, n (%)				<0.001[b]
Female	9 (69.2%)	9 (52.9%)	6 (52.9%)	
Male	4 (30.7%)	8 (47%)	25 (47%)	
Median stone size, mm^2 (min-max)	158 (78-2475)	375 (120-1564)	345 (126-1760)	0.055[a]
Stone complexity, n (%)				0.510[b]
Simple	9 (60%)	8 (47%)	19 (57.5%)	
Complex	6 (40%)	9 (52.9%)	14 (42.4%)	
Median operative time, mins. (min-max)	90 (25-125)	95 (50-155)	87.5 (24-155)	0.509[a]
Median scope time, secs. (min-max)	140 (60-220)	123 (77-600)	120 (60-1220)	0.575[a]
Sheath size, n (%)				0.032[b]
<22 Fr	11 (73.3%)	9 (50%)	11 (34.3%)	
>22 Fr	4 (26.6%)	9 (50%)	21 (61.7%)	
Median Hgb Preop-Postop, (minimum-maksimum)	0.8 (-0.2-2.10)	1 (-1.0-2.80)	1.4 (-0.9-4.8)	0.363[a]
Median Hematocrit Preop-Postop, (minimum-maksimum)	2.8 (0.8-6.8)	3.4 (-3.0-8.4)	4.2 (-4.60-11.2)	0.846[a]
Median duration of nephrostomy, days (min-max)	2 (1-3)	2 (1-2)	2 (1-3)	0.712[a]
Median hospitalization days (min-max)	1 (1-3)	2 (1-4)	1 (1-10)	0.315[a]
Result, n (%)				0.842[b]
Stone Free	13 (86.6%)	15 (88.2%)	28 (84.8%)	
Residual Stone	2 (13.3%)	2 (11.7%)	5 (15.1%)	
Complications, n, (%)				
Grade 1	1 (6.6%)	3 (17.6%)	2 (6%)	
Grade 2	2 (13.3%)	0	3 (9%)	-
Grade 3	0	3 (17.6%)	0	
Grade 4	0	0	0	
Overall complication rates	3 (20%)	6 (35.2%)	5 (15.1%)	-

SD: Standard deviation, HU: Hounsfield Unit, Fr: French, Hgb: Hemoglobin,[a] Mann-Whitney U Test, [b] Pearson Chi-square Test

Discussion

In regions that are endemic for stone disease, such as Turkey, pediatric stone disease is a significant health problem due to its high recurrence rate and the associated need for lifelong follow-up. A study done on pediatric stone disease patients reported a five-year recurrence rate of 55% after urinary stone surgery [15]. The need for repeated surgical interventions due to this high recurrence rate have highlighted the importance of minimally invasive treatments (SWL, RIRS, PCNL). The role of these procedures in the treatment of kidney stones has been established by guidelines and our daily practice. As our clinic is the referral center for Stone surgery in our area, we encounter stones with high stone burdens and complex stones more frequently.

Various studies have shown that SWL treatment is safe and effective in the treatment of kidney stones. Although SWL is a minimally invasive treatment option, its requirement for general anesthesia and radiation exposure over repeated sessions make up its most important disadvantages. Moreover, the success rate associated with this treatment method decreases with stone size, presence of multiple stones, and high stone complexity [16,17]. It has been stated that PCNL is more effective for these types of stones, and pediatric stone-free rates that vary between 67% and 100% in patients with large stones have been reported in the literature [18-22]. Ozden et al. [19] reported a success rate of 73.6% in their study where they applied PCNL monotherapy on 53 pediatric renal patients, who had a mean stone size of 654.0 (92.4). In our study, the mean stone size of our patients was 683 (564.8) and our stone-free rate was determined as 85.2%, paralleling the literature. We think that the experience of the surgeon has greater importance in the case of pediatric stone disease patients with high stone burden and complex stones in particular.

While NCCT scans are commonly used prior to PCNL surgery in adult patients, their use in the case of pediatric patients causes concerns for the physician and the parents due to radiation exposure. However, studies have shown that NCCT performed prior to PCNL facilitates the planning stage and access, especially in cases of high stone burden and complex stones [23-25]. Moreover, it was reported to provide advantages relating to the prediction of certain major complications such as a retrorenal colon [23]. At our clinic, we supplement USG with NCCT as an imaging method in cases of suspicious or inconclusive USG results, kidney anomalies on USG, staghorn and semi-staghorn calculi, and non-opaque stones. Moreover, by conducting the preoperative NCCT, we can calculate the HU values of the stones and obtain information about stone densities before the operation. Although different cut-off values have been used in studies investigating the relationship between stone density and SWL success (1000> HU and 600> HU), it has been demonstrated clearly that lower stone densities are connected to increased SWL success rates [7-10]. On the other hand, Ito et al. [11] have demonstrated the relationship between the HU value and the effectiveness of the stone fragmentation in RIRS. This study has also reported that in stone sizes of 20 mm and below both maximum and mean HU values were determinative for the duration of operation. However the relationship between the success of PCNL performed on adults and stone density is contended in the literature [12,13]. In their study, Gucuk et al. [12] reported that in contrast to SWL, lower Stone densities (HU <677.5) translated to a 2.65 fold increase in the residual stone rate following PCNL. They explained this by suggesting that lower-density stones became more non-opaque and were less visible under fluoroscopy during surgery, resulting in an increase in residual stones. On the other hand, another study determined that stone HU ratios (1000> HU-HU <1000) did not affect post-PCNL stone-free rates but the hardness of the stone prolonged the operative duration and fluoroscopy time[13]. We determined that the HU ratios of our pediatric patients did not affect PCNL success, and while the high density group with a stone density >1000 manifested longer operative durations, there were no statistically significant differences.

In line with the technological advances that took place in recent times, the shift from open surgery to minimal invasive surgery required the surgical tools to decrease in size. The reduction in sheath size lead to a decrease in blood transfusion rates [26,27]. Celik et al. [28] grouped pediatric patients in their study based on the size of the nephroscopes they used during the PCNL procedure. They reported that patients they operated using pediatric nephroscopes manifested a statistically lower fall in hematocrit values. However, although studies report decreased rates of hemorrhage in association with the decrease in sheath and nephroscope sizes, there are also studies that suggest that using adult type instruments on this age group does not increase the rate of general complications [26-29]. Adult type instruments also possess advantages due to being readily available at every center and allowing faster stone clearance during surgery in patients with higher stone burdens. In our pediatric cases, we selected dilatation sets, sheaths, and nephroscopes based on the patient's age, BMI, and stone burden.

Various studies attest to the safety and effectiveness of PCNL surgery for patients in all age groups ranging from newborn to late adolescence [4,5]. In their study, Mahmud et al. [4] performed PCNL on 29 children between the ages 0-5. In their study the median stone size was 23.6 mm (13-60 mm).

They reported a 6% complication rate and a stone-free rate of 60% in the third month following the PCNL. In another study, they performed PCNL on 20 patients between the ages 0-5 [5]. Median stone size was 33 mm (20-46 mm). They achieved a stone-free rate of 79.1% and reported an overall complication rate of 15.38%. In our study, the overall complication rate in the 0-5 age group was 23% (all the complications were grade 1 and grade 2) and the stone-free rate was determined as 84.6%. No statistical differences were determined with regard to overall complication rates and stone-free rates of PCNL surgery performed on the 0-5 age group and the other age groups. While the rate associated with the use of sheaths smaller than 22F is 73.3% for the 0-5 age group, this rate is 32.3% for patients in the 13-18 age range. The variability of this rate across age groups also demonstrated statistical significance.

One of the strengths of our study is that it is one of the very few studies that investigated the relationship between HU and success in PCNL cases. Additionally, the absence of a statistical difference between pediatric patients in the different age groups and HU groups with regard to stone size and stone complexity, which are known to affect PCNL success, can be considered another strength. The limitations of our study can be listed as being based on retrospective data, involving heterogeneity in sheath and nephroscope sizes used within age groups during PCNL operations and including a relatively low number of patients.

In conclusion, PCNL surgery is a minimally invasive treatment method that can be safely and effectively used on pediatric patients that have complex stones and high stone burdens. Based on the data from our retrospective study, we determined that stone HU values of pediatric patients who were examined using NCCT prior to PCNL did not influence operative durations, fluoroscopy times, and PCNL success. The technological advances of our time brought a gradual decrease in the size of surgical equipment used in PCNL surgery. We believe that the reduction in size of surgical equipment and increased experience in performing PCNL surgeries facilitates successful performance of this operation on every age group with increased reliability.

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Transaortic celiac plexus block: A computed tomography simulation study

Transaortik çölyak pleksus bloğu: Bilgisayarlı tomografi simülasyon çalışması

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Abstract

Aim: Transaortic celiac plexus block (CPB) is a traditional treatment method in chronic upper abdominal pain. Knowing the technique parameters before the procedure provides convenience to the physician during the block. For this purpose, we simulated the transaortic CPB with computed tomography (CT) and thus aimed to determine the main technical parameters and the risk of complications.

Methods: This study was an observational study. We analyzed one hundred, transaxial, thin section, abdominopelvic CT images and recorded morphological disturbances such as the presence of aortic mural calcification, thrombus, and aneurysm. We drew a needle insertion pathway on each of the images, at left, seven cm away from the midline in the lumbar region. Subsequently, we recorded the penetrated organs, the needle entry angle, and the distance from the skin to the needle tip. Also, we measured the appropriate entry distance and angle for successful injection in patients that we could not provide transaortic access.

Results: In the CT-simulated images, according to defined level and distance, we could reach the aorta in 73% of the patients. The mean needle entry angle and the distance from the entry point to the needle tip was 23.33 (3.36)°, 15.25 (1.20) cm, respectively, and kidney penetration was 6.9%. We were able to access aorta in remaining 27% of patients with a mean distance of needle entry point from the midline, a mean needle entry angle, and a mean distance from the entry point to the needle tip, 10.08 (1.25) cm, 34.04 (5.43)°, and 17.09 (1.32) cm, respectively. The kidney penetration rate was 44.4% in these patients.

Conclusion: In the transaortic technique used for the CPB, successful aortic penetration is not always achieved. When the access angle and distance are increased, aortic transition can be achieved, but the risk of organ injury significantly increases.

Keywords: Celiac plexus block, Computed tomography, Transaortic, Sympathetic ganglion block

Öz

Amaç: Transaortik çölyak pleksus bloğu (ÇPB), kronik üst karın ağrısında kullanılmakta olan bir tedavi yöntemidir. İşlem öncesi teknik parametrelerin bilinmesi, blok sırasında hekime kolaylık sağlar. Bu amaçla, çalışmamızda transaortik ÇPB'yi bilgisayarlı tomografi (BT) ile simüle ettik ve böylece ana teknik parametreleri ve komplikasyon riskini belirlemeyi amaçladık.

Yöntemler: Bu, gözlemsel bir çalışmaydı. 100 hastanın, transaksiyel, ince kesit, abdomino-pelvik BT görüntüleri incelendi. Aort duvar kalsifikasyonu, trombüs ve anevrizma varlığı gibi morfolojik bozukluklar kaydedildi. Her bir görüntüde, lomber bölgede, orta hattan yedi cm solda iğne giriş yolağı çizildi. Sonrasında, görüntülerde oluşan organ penetrasyonları, iğne giriş açıları ve deriden iğne ucuna olan mesafeler kaydedildi. Ek olarak, transaortik geçişle çölyak pleksusa ulaşamadığımız hastalarda başarılı enjeksiyon için uygun giriş mesafesini ve açısını ölçtük.

Bulgular: Tanımlanmış seviye ve mesafeye göre BT ile simüle edilmiş görüntülerde hastaların %73'ünde aort içerisinden geçiş sağlayabildik. Ortalama iğne giriş açısı ve giriş noktasından iğne ucuna olan mesafe sırasıyla 23,33 (3,36)°, 15,25 (1,20) cm ve böbrek penetrasyon oranı %6,9 idi. Aorta erişemediğimiz % 27 hastada yapılan yeni ölçümde, orta hattan ortalama iğne giriş mesafesi, ortalama iğne giriş açısı ve giriş noktasından hedef noktaya olan ortalama mesafe sırasıyla, 10,08 (1,25) cm, 34,04 (5,43)° ve 17,09 (1,32) cm idi. Bu hastalarda böbrek penetrasyon oranı ise %44,4'tü.

Sonuç: Transaortik ÇPB tekniğinde, her zaman, başarılı şekilde aort penetrasyonu sağlanamaz. Erişim açısı ve mesafesi arttırıldığında, transaortik geçiş sağlanabilir, ancak organ hasar riski önemli ölçüde artar.

Anahtar kelimeler: Çölyak pleksus bloğu, Bilgisayarlı tomografi, Transaortik, Sempatik ganglion bloğu

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Introduction

Celiac plexus block (CPB) is an effective treatment modality that has been used for a century in chronic visceral pain of the upper abdomen caused by chronic pancreatitis, stomach, liver and pancreatic cancer [1]. Percutaneous CPB was first described by Kappis [2] in 1919 and has undergone modifications over time. A meta-analysis of 24 articles about conventional CPB techniques has revealed good to excellent pain relief in 90% of patients in 3 months period [3]. In the transaortic approach, this ratio is reported in between 91% [4] and 93% [5]. Variations and combinations of techniques remain as means of reducing the complication and morbidity as well as increasing the success of the procedure.

The celiac plexus has a deep retroperitoneal location at the T12 and L1 vertebrae. It surrounds the abdominal aorta and is near major vital organs such as large vessels, liver, and kidneys [6-8]. Due to this particular anatomical location, it is crucial to assess parameters such as the appropriate needle placement location, angle, and depth of needle tip reaching the target. Several CPB techniques have been described to reduce the risk of organ injuries that may occur in the needle path. Fluoroscopy or computed tomography (CT)-guided percutaneous retrocrural, transcrural, transaortic, and gastric endoscopic approaches can be counted as the most commonly used methods for this purpose [6,7,9]. The goal of the procedure is to obtain adequate analgesia by providing proper distribution of the neurolytic agent around the celiac plexus via a nerve block needle [10]. The main reason for the emergence of these techniques using different needle entry points, angles, and paths is to minimize the complications and maximize the success of the injections.

The CT examination is one of the most commonly performed imaging modalities in abdominal pathologies. The great anatomical information provided by its high temporal and spatial resolutions has made CT a potent imaging method in the diagnosis of abdominal cancers such as liver, pancreas, and kidney. Nowadays, this modality has been commonly used not only for the diagnosis but also for guiding the treatment. In the literature, there are CT simulation studies made for this purpose. In light of the results obtained from these studies, new modifications are recommended for more successful injections and low complication rates [8,11].

The transaortic CPB refers to the injection of the neurolytic agent in front of the anterior wall of the aorta in the retroperitoneal space. The entrance distance defined for the transaortic technique is seven cm left from the midline at the level of L1 vertebra [12]. After skin puncture, the block needle is advanced under fluoroscopy or CT guidance. Once the target is reached, the injection is performed, and the drug surrounds the anterior and then the posterior of the abdominal aorta [13,14]. The main advantage of the transaortic approach is minimizing the risk of neurological complications arising from the spread of the neurolytic agent to the lumbar plexus or spinal cord [15]. Another advantage is that in conventional techniques, bilateral injections should be performed, whereas, in the transaortic approach, a single injection is sufficient, which reduces the risk of organ injury. Therefore, we have chosen the transaortic approach among the various CPB approaches.

In the curent study, we aimed to investigate the successful injection rate with the classical transaortic approach and to simulate the ideal way in remaining patients in whom we could not reach the aorta and to evaluate the complication rates in both circumstances. We foresee that the parameters obtained as a result of the measurements in the study will provide useful information and guidance for the practitioners performing the transaortic CPB.

Materials and methods

After approval of the Institutional Review Board (2018/15, 18/240), we analyzed the images of one hundred adult patients' transaxial, thin section (3 mm), abdominopelvic CT scans, using the Image Archiving and Communication System (PACS) of our hospital. We selected the images scanned with a pre-diagnosis of renal stone between January and October 2018. The age of the study group was determined as 40-80 years since CPB is a treatment modality used for intractable pain in upper abdominal malignancies and chronic pancreatitis usually seen in this age group. We excluded the patients who have undergone surgery in the lumbar region and patients with congenital or acquired vertebral bone pathology with any mass/cancer that could affect the subcutaneous and visceral adipose tissue. We used blocked randomization for patients' ages and genders, as they may affect the outcome of our clinical trial. This method randomizes several patients at a time in such a way as to provide that equal numbers are allocated to each group, instead of randomizing each patient separately. Thus, we have chosen 50 female, and 50 male patients among the 100 patients who met the inclusion criteria and the mean ages of these male and female patients were equal.

Detailed measurements were performed using a special software (RadiAnt DICOM Viewer 4.6.5, Medixant, Poznan, Poland) on thin section (3 mm) images acquired from two separate CT devices with 64- and 320- detectors (Aquilion; Toshiba Medical Systems, Otawara, Japan) of the same brand. All calculations were performed at the level of the L1 vertebral body. On CT images, the needle entry angle and the distance from the entry point to needle tip were evaluated separately for each patient. The possible differences and possible relationships of these measurements for both genders were statistically evaluated. Additionally, when seven cm distance from the midline was accepted as the optimal entry point, patients who could not be accessed through the aorta were also identified. In those patients, technique parameters (the needle entry angle and the distance from the skin surface to needle tip) and the optimal needle trace passing through the aorta, which is necessary for an optimal plexus block was redrawn. For this purpose, in the simulated transaortic CPB procedure, vital abdominal organ injuries such as kidney and lung penetrations in the needle advancement traces were also examined (Figure 1). Since the use of the transaortic CPB technique is contraindicated, patients with an aortic aneurysm and extensive mural calcification were recorded.

CT Parameters

In the current study, the needle entry angle and the distance from the entry point to needle tip were evaluated as the main parameters. The measurements were performed on thin-

section CT images by simulating a transaortic CPB at the level of the L1 vertebral body (Figure 2.a). As described in the literature, a distance of seven cm from the midline was marked in the left lumbar region by the classical transaortic CPB technique [12,16]. The main line was drawn between the defined point and the celiac plexus region, passing through the aorta. The angle between the main line and the vertical line passing through the middle of the spinous process was recorded as the needle entry angle. The distance from the entry point to the needle tip was measured by calculating the length of the main line.

Statistical analysis

After the data were transferred to the computer environment, the SPSS 21.0 package program was used for the detailed analyses. Descriptive statistics were given as number, percentage, mean, standard deviation, minimum, and maximum values. The Kolmogorov-Smirnov test was applied to determine the consistency of continuous data to normal distribution. T-test was used for the analysis of continuous data that conforms to the normal distribution, and the Fischer's Exact Test was performed for the comparison of the discrete variables. Statistical significance was accepted as $P<0.05$.

Results

The study group consisted of 50 female and 50 male patients, and the mean age was 60 (12.2) (40 - 80) years. In 100 patients enrolled in the study, transaortic CPB was simulated on thin-section CT images. The needle entry angle and the depth required by the needle tip were measured using special software for each patient. All measured parameters and their distribution according to gender are shown in Table 1 in detail. The ratio of extensive aortic mural calcification was observed in 2% of the patients in the CT-simulated images (Figure 2.b). We could not reach aorta with the simulation of classic transaortic CPB in 27% of patients. Among this group, 16 were male, and 11 were female, and there was no statistically significant difference between the genders regarding this subject ($P=0.36$) (Table 1).

When the needle entry point was seven cm left to the midline at the L1 level in the lumbar region, we could reach the aorta in 73% of the patients (n:73). In these patients, the mean needle entry angle was found as 23.33 (3.2)° (ranging 16.3 - 33°). This value was 22.98 (2.8)° in males and 23.69 (3.52) in females. The distance from the entry point to the needle tip was 15.25 (1.2 cm) (ranging 11.81 – 19.43 cm) in this group. This value was found as 15.41 (1.12) cm and 15.09 (1.29) cm in males and females, respectively. There was no statistically significant difference between the patients regarding the needle entry angle and the distance from the entry point to the needle tip ($P=0.26$, $P=0.18$). The ratio of kidney penetration was observed in 6.9% of the patients in the CT-simulated images (Table 2).

We tried to obtain an ideal transaortic approach by changing our entry point and angle in the remaining 27% of patients whose aorta could not be reached with classic transaortic CPB in the CT simulation. When the optimal needle trace passing through the aorta was found on those patients, a cross line was drawn to the skin. The distance between the skin surface and midline was noted. Instead of seven cm distance defined for the classic transaortic CPB, we found the distance 10.08 (1.25 cm) (ranging 8 – 13.46 cm). The low needle entry angle was 34.04 (5.43)°, and the distance from the entry point to needle tip was 17.09 (1.32) cm in those patients. The measured parameters were shown in Table 3. Additionally, major organ penetrations were reevaluated in those patients with modified traces on CT images. In these images, we did not observe any lung or liver penetration, while in 12 patients (44.4%), we observed kidney penetration (Figure 2.c).

Table 1: The distribution of age, number of extensive aortic mural calcification, number of patients in whom aorta was not reached at 7 cm, and their statistical relationship with gender in the study group

	Total (n: 100)	Male (n: 50)	Female (n: 50)	*P*-value
Age Mean (SD), year	60.00 (12.09)	60.00 (12.15)	60.00 (12.15)	1
Number of extensive aortic mural calcification (%)	2 (2%)	1	1	1
Number of patients in could not be reached at 7 cm (%)	27 (27%)	16	11	0.36

n: Number of patients, SD: Standard deviation

Table 2: Needle entry angle, distance between the skin surface and the needle tip, and number of kidney penetration, and their statistical relationship with gender in the study group

	Total (n: 73)	Male (n: 34)	Female (n: 39)	*P*-value
Needle entry angle (SD), degree	23.33 (3.36)	22.98 (2.81)	23.69 (3.52)	0.26
Distance between skin surface and needle tip (SD), cm	15.25 (1.20)	15.41 (1.12)	15.09 (1.29)	0.18
Number of kidney penetration (ratio)	5 (6.9%)	0	5	0.06

n: Number of patients, SD: Standard deviation

Table 3: The detailed measurements of the patients in the study group whose aorta cannot be reached in simulations using the classic distance of 7 cm from the middle line

	Number of patients in whom aorta was not reached at 7 cm (n: 27)
Distance from midline (SD), cm	10.08 (1.25)
Needle entry angle (SD), degree	34.04 (5.43)
Distance between skin surface and needle tip (SD), cm	17.09 (1.32)
Number of kidney penetration (ratio)	12 (44.4%)

n: Number of patients, SD: Standard deviation

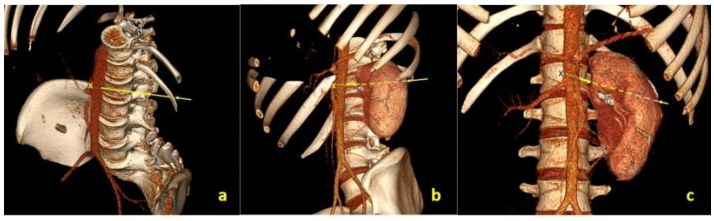

Figure 1: Three Dimensional oblique coronal (a and b) and coronal (c) volume-rendered images demonstrate the needle trace in an transaortic celiac plexus block. Kidney penetration is seen as figure b and c. (X= celiac plexus location)

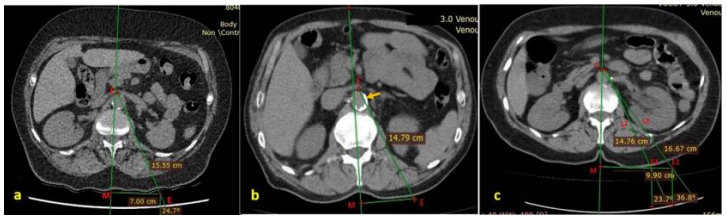

Figure 2: Axial thin section noncontrast abdomino-pelvic CT images at L1 vertebra level; a. Needle entry point (E1) is 7 cm left from the midline (M) in accordance with the classical transaortic celiac plexus block technique. A line was drawn between E and the celiac plexus (C), passing through the aorta. The angle between this line and the vertical line passing through the middle of the spinous process was recorded as the needle entry angle. b. Yellow arrow points extensive aortic mural calcification. c. Needle entry point in classical transaortic (CPB) technique, the main line is not passing through the aorta (L1). When a new line (L2) is drawn from the celiac plexus oppositely which is passing through the abdominal aorta, the new (optimal) needle entry point is located at a point farther from the midline (7 cm vs. 9.9 cm). The needle entry angle is 23.7° for L1, while it is 36.8° for L2. The distance from entry point to needle tip (C) is 14.76 cm for L1 and it is found as 16.67 cm for L2. This trace is penetrating the left kidney as a complication. (M= Midline, C= Celiac plexus, E1= Entry point 1, E2= Entry point 2, L1= Line 1, L2: Line 2)

Discussion

The main significant result of our study was that the abdominal aorta could not always be reached with the defined transaortic approach. In these patients, the distance of the needle to the midline and the angle of entry can be increased so that aortic passage can be achieved, but this increases the risk of organ injury.

There are very few studies on the radiographic anatomy of CPB in the literature [15,17]. Previous radiological studies of the CBP were related to conventional antecrural or retrocrural techniques [8,11]. To the best of our knowledge, this is the first CT simulation study for transaortic CPB. In the current study, we investigated the specific technical parameters related to transaortic CPB by simulating the procedure on CT images to estimate the success and complication rates.

The most common clinical complication of the CPB is back pain and diarrhea, and the worst one is the increased risk of retroperitoneal bleeding due to iatrogenic aortic puncture, which may occur up to 0.5% in patients with hypertension or coagulopathy [16]. Since this is a radiological study, we could not evaluate clinical complications. However, according to the simulation results, we were able to evaluate the risk of vital organ and anatomical structure injuries. In the current study, the rate of kidney penetration was 6.9% in the classical transaortic approach. However, this rate was 44.4% in patients whom we could not reach the aorta by the classical approach and determined a more lateral entry point at the skin. In the CT simulation study of retrocrural CPB of 108 patients applied by Gabriela et al. [11], renal injury rates were 0.92% at 4.5 cm, and 23.25% at 9 cm left from the midline. On the other hand, in the transaortic CPB study performed by Abbas et al. [18], no kidney damage was observed in any patient. Such a significant difference between radiological study and clinical study may indicate that every radiologically evaluated renal penetration may not occur in clinical practice, or even if it occurs, it may not manifest clinically. Prospective randomized clinical trials are needed on this issue.

The most severe complications to be recognized and treated in the transaortic CPB are those associated with aortic injury. Therefore, this procedure is contraindicated in patients with an aortic aneurysm, extensive mural calcification, and mural thrombus was observed [16]. In the study, we observed 2% extensive mural calcification, 17% mild mural calcification, no aortic aneurysm, and thrombus. Therefore, it is keenly recommended to examine the anatomical structures and changes in the celiac region with CT before the procedure.

The most important information given in the results of the study is the anatomic variability, complexity, and individuality of the region. In patients with upper abdominal tumors, deterioration of celiac anatomy, or growth in lymph nodes is common. These changes can sometimes make the procedure impossible. For this reason, CT simulation of transaortic CPB before administration increases the chance of successful injection and reduces the risk of complications. Alternative techniques such as an epidural catheter, spinal port, and especially splanchnic block, can be considered if there is a risk observed in the pre-procedural CT simulation.

There were some limitations to our study. Firstly, direct lines we used in simulated images may not reflect the process that was very dynamic, such as needle movement. The second limitation although it is known that the retroperitoneal anatomy does not show a significant change with postural changes, the fact that our measurements were performed on CT images taken in supine position could be seen as a limitation for the CPB performed in the position of prone or lateral decubitus. Besides, we used CPB for the treatment of upper abdominal and visceral pain, but the patients we examined were not selected from this population, and this can be counted as the third limitation. In our study on CT images taken within the specified date range, the sample size was small due to rigid inclusion criteria, and since this study was performed on existing patient images, the height and weight information of the patients could not be reached, and these can be considered as other limitations.

Conclusion

In case of abdominal tumors, there may be alterations in the shape and size of the tumor and personal anatomical variations in the needle path do not allow us to administer the transaortic CPB technique always successfully. However, in the light of our initial and preliminary reports, we can suggest that modification in the needle entry point and angle may result in accurate injection, but on the other hand, it can significantly increase the risk of organ injuries.

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Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent

Makrosiklik-iyonik gadolinyum-bazlı kontrast ajan ile tekrarlanan uygulamalar ile T1 ağırlıklı kontrastsız manyetik rezonans görüntülemedeki sinyal intensite artışı

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Ethics Committee Approval: University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital local ethical committee, 15.10.18, 55/14.
Etik Kurul Onayı: Sağlık Bilimleri Üniversitesi Yıldırım Beyazıt Dışkapı Eğitim ve Araştırma Hastanesi lokal etik komitesi, 15.10.18, 55/14.

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Abstract

Aim: Gadoterate meglumine is a macrocyclic-ionic gadolinium-based contrast agent (GBCA) which is using in the magnetic resonance imaging (MRI). This study aims to determine the relationship between the signal intensity (SI) increase in the dentate nucleus (DN), pons (P), globus pallidus (GP), thalamus (T) and use gadoterate meglumine by repeated brain MRI in lung cancer patients.

Methods: The study was designed as a retrospective cohort study. The mean SIs of the DN, P, GP, and T and the cerebrospinal fluid (CSF) were measured in the unenhanced T1-weighted (T1w) images of the first and last MRIs of patients who underwent at least three brain MRI examinations with gadoterate meglumine. DN, P, GP, T SIs were divided by values obtained from CSF to standardize the SI measurements. The DN, P, GP, T SIs and DN/CSF, P/CSF, GP/CSF, T/CSF ratios were compared the first and the last MRI examinations.

Results: Our study revealed significant increases in DN, P, GP, and T SIs (P<0.001, P<0.001, P<0.001 and P=0.024, respectively). DN/CSF, P/CSF, GP/CSF, and T/CSF ratios were also significantly increased (P<0.001, P<0.001, P<0.001 and P=0.022, respectively). The number of examinations had a moderately strong positive correlation with in the DN/CSF ratio and a strong positive correlation with in P/CSF ratio (P<0.001 and P<0.001, respectively). There was a weak positive correlation between MRI intervals and in P/CSF ratio (P=0.037).

Conclusion: Our study suggested an increase in the first and the last MRI in DN, P, GP and T SIs related to the number and intervals of repeated examinations of a brain MRI with gadoterate meglumine among patients with lung cancer.

Keywords: Gadoterate meglumine, Brain, Magnetic resonance imaging, Signal intensity

Öz

Amaç: Manyetik rezonans görüntülemede (MRG) kullanılan makrosiklik-iyonik gadolinium- bazlı kontrast (GBKA) ajandır. Bu çalışmanın amacı gadoterat meglumin ile tekrarlıyan beyin MRG yapılmış akciğer kanserli hastalardaki dentat nucleus (DN), pons (P), globus pallidus (GP), talamusdaki (T) sinyal intensite (Sİ) artımı ile ilişkisini belirlemektir.

Yöntemler: Çalışma retrospektif kohort çalışması olarak tasarlanmıştır. Gadoterat meglumin ile en az üç ve daha fazla beyin MRG incelemesi yapılmış hastaların ilk ve son kontrastsız T1 ağırlıklı MRG incelemelerindeki DN, P, GP, T ve beyin omurilik sıvısındaki (BOS) ortalama Sİ'leri ölçüldü. DN, P, GP, T Sİ değerleri, Sİ ölçümlerini standartlaştırmak için BOS'dan elde edilen değerlere bölündü. DN, P, GP, T Sİ'leri ve DN/BOS, P/BOS, GP/BOS, T/BOS oranları ilk ve son MRG incelemelerinde karşılaştırıldı.

Bulgular: Çalışmamızda DN, P, GP ve T' Sİ'lerinde anlamlı şekilde artış saptandı (sırası ile P<0,001, P<0,001, P<0,001 ve P=0,024). DN/BOS, P/BOS, GP/BOS, T/BOS oranlarının anlamlı şekilde arttığı tespit edildi (sırası ile P<0,001, P<0,001, P<0,001 ve P=0,022). Çekim sayısının; DN/BOS oranı ile arasında orta düzeyde; P/BOS oranı ile arasında yüksek düzeyde pozitif yönlü korelasyon saptandı (sırası ile P<0,001 ve P<0,001). MRG çekim aralıkları ve P/BOS oranı ile arasında hafif düzeyde pozitif yönlü korelasyon mevcuttu (P=0,037).

Sonuç: Çalışmamızda akciğer kanserli hastalarda gadoterat meglumin ile tekrarlayan beyin MRG çekimlerinde, çekim sayısı ve aralıkları ile ilişkili olarak DN, P, GP ve T Sİ'lerinde ilk ve son MRG'ler arasında bir artış olduğu gösterilmiştir.

Anahtar kelimeler: Gadoterat meglumin, Beyin, Manyetik rezonans inceleme, Sinyal intensite

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Introduction

Gadolinium-based contrast agents (GBCAs) are extensively used to enhance contrast in magnetic resonance imaging (MRI). GBCAs enhance the tissue contrast by virtue of their shortening effect of the T1 relaxation time of the living tissues. Gadolinium (Gd) is a rare- earth heavy metal which is highly toxic to humans in its free form and is used as bound by ligands when used as a contrast agent. It is bound to chelating agents to form linear forms (gadodiamide, gadopentetate dimeglumine and gadoxetate disodium) and macrocyclic (gadoteridol, gadobutrol and gadoterate meglumine). While macrocyclic molecules, form a completely enclosed cage enveloping the Gd ion, linear molecules form partial cages wrapped around the Gd ion and are not completely closed [1,2]. Furthermore, GBCAs are subgrouped as ionic and non-ionic based on their charge. As the electrostatic interaction of ionic GBCAs with chelates is more intense, they are considered more stable than non-ionic agents [1].

In the recent few years, many studies reporting a concentration-dependent deposition of Gd in the brain, characterized by high signal intensities (SI) on unenhanced T1-weighted (T1w) images, have been published. Previous studies showed that Gd mostly accumulates in globus pallidus (GB) and dentate nucleus (DN) [1,2]. There is a well-documented association between T1w image hyperintensities in the GP and DN and multiple administrations of linear GBCAs [3-7]. On the other hand, macrocyclic GBCAs are known to not accumulate in the brain and are therefore considered to be extremely safe. However, the latest studies in the literature have contradicted previous knowledge regarding the safety of the macrocyclic GBCAs. It has been shown that administration of gadobutrol, a macrocyclic-non-ionic GBCA, is also associated with T1w SI changes in the brain [8,9]. Moreover, Rossi Espagnet et al. [10] reported that macrocyclic-ionic GBCA gadoterate meglumine caused an increase in the brain T1w SI in a pediatric population.

However, there is a paucity of studies specifically addressing a possible association between T1 hyperintensities in the brain and multiple administrations of gadoterate meglumine in the adult population.

The aim of the current study was to investigate the relation between the SI increase in the DN, P, GP, T and the use gadoterate meglumine by repeated brain magnetic resonance imaging (MRI) in lung cancer patients.

Materials and methods

Patient population

The ethical compliance of this study was approved in accordance with the Helsinki Declaration by the Hospital Local Ethics Committee, Ankara, Turkey. The medical records of a total of 758 patients who were diagnosed with lung cancer and followed exclusively at the medical oncology service of our hospital between September 2015 and January 2019 were retrospectively assessed. Among patients who underwent at least three MRI examinations after intravenous gadoterate meglumine administration, those that met the inclusion criteria were enrolled. Inclusion criteria were as follows: (a) unenhanced T1w images were obtained before the first GBCA administration; (b) all of the consecutive MR imaging examinations were performed exclusively at our institution in the same MRI scanners. The exclusion criteria were as follows: (a) being examined at another hospital using GBCAs; (b) patients who were found to have undergone contrast-enhanced MRI examinations with contrast material containing intravenous or intraarticular gadolinium; (c) patients with a brain mass; (d) patients with brain metastasis; (e) patients with Alzheimer's disease; (f) history treatment of radiation; (g) history of the metabolic disease: (h) history of metal toxicity; (ı) history of multiple sclerosis; (j) history of total parenteral nutrition containing manganese; (k) history of nephrogenic systemic fibrosis; (l) history of brain stroke, or history of brain ischemia; (m) patients with laboratory findings consistent with renal or liver failure in simultaneous biochemical studies with the latest MRI examination; (n) patients with artifacts precluding a proper MRI examination.

A total of 61 patients (mean 57.85 years; age range, 18–69 years) with available data on the first and the last examinations with unenhanced T1-weighted images were included.

Imaging acquisition

All MRI were performed using two 1.5T MRI scanners (Magnetom, Aera, Siemens, Erlangen, Germany) and Philips Achieva (Philips Medical Systems, Eindhoven, The Netherlands) with a standard head coil.

The brain MR protocol included axial T1w, axial T2-weighted imaging, sagittal fluid-attenuated inversion recovery imaging, and axial, sagittal, coronal contrast-enhanced T1w. The axial unenhanced T1-weighted spin-echo images were obtained using the following parameters: repetition time (TR)/echo time (TE): 348/8.9 ms, voxel size: 0.7x0.7x0.5 mm, the field of view (FOV): 23x23 cm, slice thickness: 5 mm. All patients' measurements were performed over the axial unenhanced T1w spin-echo sequence.

Gadoterate meglumine is the only GBCA used at our institution for all contrast-enhanced MRI studies. Contrast-enhanced T1w images were obtained after intravenous injection of a standard dose of 0.1 mmol/kg of body weight of gadoterate meglumine (Dotarem®, Guerbet, Istanbul, Turkey).

Image analysis and measurements

MRI evaluations were performed on a picture archiving and communication system (Extreme PACS, Ankara, Turkey). Quantitative analysis was conducted by two radiologists (R.P.K. and M.Ö. with 10 and 7 years of experience, respectively), who were blinded to the serial number of the MRI scan. By consensus, they used the unenhanced T1w images of each patient (mean, 5 mm; range, 4–7 mm) circular region-of-interest (ROI) measurements of mean SI as previously described [3]. All of the ROI measurements were manually drawn.

SIs were quantified from the neuroanatomic regions of DN in pink and pons (P) in blue (Figure 1 a), ROIs were drawn at the left DN, P in the first (Figure 1 b) and the last unenhanced T1w images (Figure 1 c). SIs were quantified from the neuroanatomic regions of GP in red and thalamus (T) in green (Figure 2 a), ROIs were drawn at the left GB and T in the first (Figure 2 b) and the last unenhanced T1w images (Figure 2 c).

SIs were quantified from the neuroanatomic region of the cerebrospinal fluid (CSF) at the fourth ventricle level in

yellow (Figure 3 a), ROIs were drawn at the CSF in the first (Figure 3 b) and the last unenhanced T1w images (Figure 3c). Axial T2-weighted images were used as guidelines to confirm the correct placement of the ROIs.

DN, P, GP, T mean SIs were divided by mean values obtained from CSF to standardize the SI measurements as previously described [11]. The DN, P, GP, T SIs and DN/CSF, P/CSF, GP/CSF, T/CSF ratios were compared the first and the last MRI examinations.

Statistical analysis

The smallest significant difference that can be accepted between the positive and negative groups of the test in the T1 sequence of DN, one of the regions to be examined, was calculated as 26 [6], at least 23 cases for 5% Type I error and 90% power.

Statistical analysis was performed using SPSS Version 24 (SPSS Inc., Armonk, NY, USA). The data were analyzed using Kolmogorov–Smirnov, and Skewness–Kurtosis tests for normal distribution. The temporal change of the data was compared with the paired t-test. Categorical variables were compared with quantitative data using the Mann-Whitney U test; quantitative data were compared with one another using the Spearman correlation test. Mean and standard deviation values were used for analysis. *P*-values less than 0.05 were considered statistically significant.

Results

Demographic and characteristics of study population

The study population had a mean age of 57.85 years; 67.2% were women. The mean frequency of MRI examinations was 3.31 (0.46), with at least three and at most five MRIs having been taken. The mean interval between two MRI examinations was 26.28 (4.81) months, with the shortest interval being 16 months and the longest 34 months.

MRI Results

There were a significant increase in the SIs of DN, DN/CSF ratio, P, P/CSF ratio, GP, GP/CSF ratio, T and T/CSF ratio ($P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P=0.024$ and $P=0.022$, respectively). The largest SI difference was between DN and GP; when proportioned to CSF, the largest difference was found in DN/CSF ratio and P/CSF ratio (Table 1).

The differences in DN/CSF, P/CSF, GP/CSF, and T/CSF ratios were similar in men and women ($P=0.440$, $P=0.396$, $P=0.054$ and $P=0.099$, respectively) (Table 2).

No correlation was found between age and differences ratios of DN/CSF, P/CSF, GP/CSF, T/CSF ($P=0.675$, $P=0.955$, $P=0.142$ and $P=0.607$, respectively).

The number of examinations had a moderately positive correlation with the DN/CSF ratio and a strongly positive correlation with the P/CSF ratio ($P<0.001$ and $P<0.001$, respectively). No correlation was found between the ratios in GP/CSF and T/CSF and examination frequency ($P=0.506$ and $P=0.051$, respectively). There was a weakly positive correlation between MRI examination intervals and P/CSF ratio ($P=0.037$). No correlation was found between MRI examination intervals and ratios in DN/CSF, GP/CSF, and T/CSF ($P=0.902$, $P=0.215$ and $P=0.164$, respectively) (Table 3).

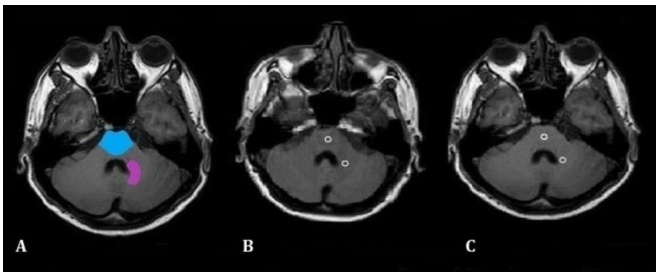

Figure 1: Axial unenhanced T1-weighted images demonstrating the anatomical locations of nucleus dentatus in pink and pons in blue (A), and the exact locations of the region of interest (ROI) where the measurements were performed at the left dentate nucleus and pons in the first (B) and the last MRI (C) examinations of the patient

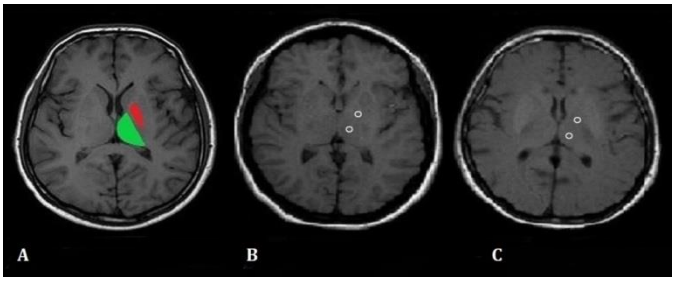

Figure 2: Axial unenhanced T1-weighted images demonstrating the anatomical locations of globus pallidus in red, and thalamus in green (A), and the exact locations of the region of interest (ROI) where the measurements were performed at left globus pallidus and left thalamus in the first (B) and the last MRI (C) examinations of the patient

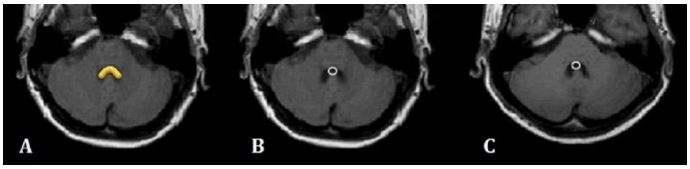

Figure 3: Axial unenhanced T1-weighted images demonstrating the anatomical locations of the fourth ventricle in yellow (A), and the exact locations of the region of interest (ROI) where the measurements were performed in the first (B) and the last MRI (C) examinations of the patient

Table 1: SIs and ratios differences in the first and last MRI examinations

	First MRI examination Mean (SD)	Last MRI examination Mean (SD)	Difference Mean (SD)	*P*-value *
DN	269.26 (3.16)	283.33 (12.95)	14.07 (13.51)	<0.001*
DN/CSF	3.45 (0.29)	4.25 (0.24)	0.8 (0.37)	<0.001*
P	277.02 (3.4)	280.84 (1.62)	3.82 (4.29)	<0.001*
P/CSF	3.28 (0.44)	4.17 (0.25)	0.88 (0.51)	<0.001*
GP	227.95 (2.25)	232.51 (1.41)	4.56 (2.64)	<0.001*
GP/CSF	2.51 (0.28)	3.22 (0.18)	0.7 (0.31)	<0.001*
T	262.79 (1.38)	263.44 (1.68)	0.66 (2.21)	0.024*
T/CSF	3.63 (0.29)	3.76 (0.32)	0.13 (0.43)	0.022*

* Paired t-test, P values less than 0.05 were considered statistically significant, SD: Standart deviation, MRI: Magnetic resonance imaging, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Table 2: The ratios differences according to the gender

	Gender		*P*-value *
	Female (n=41) Mean (SD)	Male (n=20) Mean (SD)	
DN/CSF	0.78 (0.39)	0.84 (0.31)	0.440*
P/CSF	4.29 (4.02)	2.85 (4.76)	0.396*
GP/CSF	0.64 (0.32)	0.85 (0.26)	0.054*
T/CSF	0.20 (0.42)	0.02 (0.42)	0.099*

* Mann-Whitney U, SD: Standard deviation, P values less than 0.05 were considered statistically significant, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Table 3: Correlation of age, number of MRI and time interval in the ratios

	Age		Number of MRI		Time interval	
	r	*P*-value	r	*P*-value	r	*P*-value *
DN/CSF	0.055	0.675*	0.490	<0.001*	-0.016	0.902*
P/CSF	-0.007	0.955*	0.577	<0.001*	0.268	0.037*
GP/CSF	-0.190	0.142*	0.087	0.506*	-0.161	0.215*
T/CSF	0.067	0.607*	0.251	0.051*	0.181	0.164*

* Spearman correlation, r: Correlation coefficient, P values less than 0.05 were considered statistically significant, MRI: Magnetic resonance imaging, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Discussion

More than 30 million examinations are performed with GBCAs and more than 300 million doses are used each year worldwide [12,13]. Until Marckmann et al. [14] reported that some GBCAs could cause nephrogenic systemic fibrosis (NSF) in patients with renal failure in 2006, GBCAs have been

extremely popular in that they were safe. NSF is a potentially morbid and fatal systemic disorder with skin and internal organ involvement, which is characterized by progressive extensive fibrous tissue accumulation following GBCAs use in patients with acute or chronic renal failure [15]. Fortunately, no new cases of NSF have been reported after the renal glomerular filtration rate assessment prior to GBCAs administration became a routine application. Thus, the perception of safety regarding GBCAs continued. However, in 2014, Kanda et al. [3] pointed out that GBCAs might be the cause of increased SI of DN and GB on unenhanced T1-weighted images of patients with normal renal function undergoing contrast-enhanced MRI. These increases correlated with the number of contrast-enhanced MRI examinations. Subsequent autopsy studies showing the accumulation of Gd in many tissues, including brain have prompted a review of the safety of GBCAs [16-18]. It is still unclear why, to what extent, and in which organs does Gd accumulate and how important is this accumulation [19]. Although brain Gd accumulation is considered not to cause asymptomatic clinical presentation, the heavy-metal family (manganese, iron, and copper) to which Gd belongs has been implicated in the development of parkinsonism by accumulating in the brain [19,20].

Although it has been formerly shown that linear GBCAs accumulate in brain tissue and cause the appearance of hyperintensity in T1w unenhanced examinations, there are still various views for the accumulation of macrocyclic GBCAs in the brain [1]. Radbruch et al. [11] compared the groups that underwent multiple examinations with linear-ionic GBCA (gadopentetate dimeglumine) and gadoterate meglumine and reported that gadopentetate dimeglumine caused an SI increase owing to its accumulation in DN and GP. Robert et al. [21], in an experimental study on rats, compared subjects administered repeated linear-nonionic (gadodiamide) and gadoterate meglumine to show that the group that received gadodiamide had hyperintensity in DN while there was no change in the group that received gadoterate meglumine. Ryu et al. compared linear-ionic GBCA (gadopentetate dimeglumine) and gadoterate meglumine in a pediatric population and showed that gadopentetate dimeglumine caused hyperintensity in DN and GP whereas gadoterate meglumine did not [22]. In a study on rats, Lohrke et al. [23] reported some 15-time higher brain tissue concentration of linear GBCAs compared to macrocyclic GBCAs and reported that Gd's chelating stability played an important role in this observation. Lee et al. [24], on the other hand, reported no intensity increase in DNs and GPs of patients that undergone at least 2 MRI examinations with macrocyclic-ionic GBCA. Renz et al. [25] compared linear-ionic GBCA (gadopentetate dimeglumine) and macrocyclic-nonionic GBCA (gadobutrol) among pediatric patients who underwent more than three examinations with GBCA; they reported hyperintensity in both GP and DN in both groups. They stressed that macrocyclic GBCAs caused hyperintensity as much as linear GBCAs. Stojanov et al. [8] detected hyperintensity in DN, GP, and P following multiple macrocyclic-nonionic GBCA (gadobutrol) use in patients with multiple sclerosis. Rossi Espagnet et al. [10] in a study on pediatric patients, revealed that gadoterate meglumine led to hyperintensity at the level of GP, DN, and P. Kartamihardja et al. [26] in an animal experiment, showed that Gd deposits forming in macrocyclic-ionic GBCA administered subjects were excreted from the brain over time whereas the deposits remained in substantial quantities in those who were administered linear-nonionic GBCAs. In an autopsy study, Murata et al. described Gd accumulation in the brains of patients administered linear GBCAs and macrocyclic GBCAs, with the most substantial accumulation having been in GP and DN [18]. We detected the highest SI suggesting brain gadolinium accumulation in DN and GP among patients that underwent multiple MRI with gadoterate meglumine. The difference between linear GBCAs and macrocyclic GBCAs reported in the literature may basically stem from macrocyclic GBCAs accumulating in the brain to a very small extent. Such studies show variations with respect to age, race, and selected patient groups. It should be remembered that the GBCAs doses are administered by patient weight and weight-adjusted contrast material doses play a significant role. Furthermore, there is no standardization of measurement parameters between those studies. Compared to CSF, the largest difference ratios were found for DN/CSF and P/CSF; although we considered that this difference may have been due to blood flow coming to those regions and, hence, agent's excretion, more studies are needed in this subject.

McDonald et al. [27] reported that the cumulative Gd dose showed a strong correlation with tissue Gd concentration in basal ganglia and posterior fossa as well as changes in T1w SI following at least four GBCA administrations. Radbruch et al. [11] reported that SI increased in DN and GP in T1w images originated from administering serial linear-ionic GBCA and was correlated to the number of examinations. Errante et al. [28] showed a relationship in the form of regression between the number of MRI examinations taken with linear-nonionic GBCA (gadodiamide) and increased SI. We detected a positive correlation between the number of examinations and in DN/CSF ratio and P/CSF ratio but not with the ratios in GP/CSF and T/CSF. We believe that tissue contrast builds up to increase SI values with each examination over time.

Jost et al. [29], in a rat study, reported that SI increases in DN and P by 24 hours after GBCAs administration. Stojanov et al. [8] found out that a greater rate of hyperintensity as the interval between the examinations shortened among patients with multiple sclerosis who were administered macrocyclic-nonionic GBCA (gadobutrol). Frentzel et al. [30] reported that Gd dissociated from linear chelates after a 15-day period; linear Gds' dissociation rate was greater than that of macrocyclic forms; macrocyclic chelates were more stable than linear ones. We detected a correlation between MRI examination interval and in P/CSF ratio but not with ratios in DN/CSF, GP/CSF, and T/CSF. This may be due to excretion of GBCA from different parts of the brain over time due to its half-life. Furthermore, it may be related to time to being excreted from tissues with GBCA stabilities.

The retrospective nature of the study created some limitations. All measurements were done manually over the images obtained by the 1.5-T MRI device by standard brain protocol sections. Acquisition of thin, continuous sections with a 3T MRI device may enable obtaining images with better

resolution, providing more precise results. GBCA doses are adjusted by patients' body weight. As we did not know the patients' body weights, we had no information about the total dose of the Gd.

Conclusion

In conclusion, our study shows the increase in SI in the DN, GP, P, and T due to the use of gadoterate meglumine in unenhanced T1w images. Although its clinical effects remain unknown, for the time being, one should be aware of Gd accumulation. We are of the opinion that doctors should be cautious about the use of macrocyclic-ionic GBCA, gadoterate meglumine, which is considered safe. This subject should be further studied by multicenter standardized trials.

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Pressure ulcer rates of stroke patients in a public rehabilitation hospital and training rates of nurses for pressure ulcer

Bir kamu rehabilitasyon hastanesindeki inme vakalarının bası yarası oranları ve hemşirelerin bası yarası eğitim oranları

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Abstract

Aim: Stroke is a brain vascular disease that affects millions of people in the world every year and causes disability. Complications following a stroke are known to increase hospital stay and patient care costs. A complication of stroke, pressure ulcer, can be avoided with education of the caregiver. That is why we aimed to investigate the rates of pressure ulcers of patients who were hospitalized in a public rehabilitation hospital because of stroke. Secondary aim of this study is to investigate the in-service trainings of the nurses about pressure ulcers.

Methods: This is an observational study. The files of inpatient stroke cases were retrospectively analyzed for dates between 01/01/2016 and 12/31/2018 and the data were collected. Education service files are analyzed for in-service trainings about pressure ulcers. Percentages were calculated for statistical analysis.

Results: Of the 3640 patients hospitalized in our hospital, 1776 had stroke (48.80%). The number of patients with acute stroke was 1216 (68.47%). The mean number of days of hospitalization was 27.6 days. When the demographic characteristics of the patients were examined, 1005 of the inpatients were male (56.59%), 771 were female (43.41%). The mean age of the male patients was 64.18 and the mean age of the female patients was 68.78 respectively. When the risk factors for stroke were examined, 59.74% of the hospitalized patients had hypertension (HT), 25.16% had diabetes mellitus (DM), 13.56% had hyperlipidemia (HL), 15.03% had cardiac disease, 6.41% had urinary infection, 3.71% had pulmonary infection, 0.5% had deep vein thrombosis, and 0.56% had malignancy. When the rate of pressure ulcers were examined, the number of stroke patients with pressure ulcers was 123 (6.92%) and no new pressure ulcers were observed during hospitalization. The rate of stroke patients with pressure ulcers among all pressure ulcer patients was calculated as 32.97%. The most common anatomic localization was sacrum 65 (52.84%) while the least common localization was elbow region with 1 patient (0.81%). The in-service trainings given to the nurses for pressure ulcers were 2 per year and the rate of nurses attending the training was determined as 71.5%. The number of trainings for medical companions was 12 per year and the participation rate to the training was 57.3%.

Conclusion: The incidence of pressure ulcers in stroke patients was determined as 6.92% and the most frequent localization was sacrum. The fact that the rate of new pressure ulcer opened in the hospital is zero indicates that in-service training and awareness about pressure ulcers in the rehabilitation hospital is sufficient.

Keywords: Stroke, Pressure ulcer, Rehabilitation

Öz

Amaç: İnme, her yıl dünyadaki milyonlarca insanı etkileyen ve yeti yitimine neden olan bir beyin damar hastalığıdır. İnme sonrası komplikasyonların hastanede kalmayı ve hasta bakım maliyetlerini arttırdığı bilinmektedir. İnme komplikasyonlarından biri olan bası yaraları bakım verenin eğitimi ile önlenebilir. Bu çalışmanın amacı bir kamu rehabilitasyon hastanesinde inme nedeniyle yatarak rehabilitasyon gören hastaların bası yarası oranlarını ve hemşirelere yönelik verilen bası yarası eğitim oranlarını araştırmaktır.

Yöntemler: Çalışmamız gözlemsel bir çalışmadır. 3 yıl boyunca (01.01.2016-31.12.2018), hastanemizde yatarak inme tedavisi gören hastaların dosyaları retrospektif olarak taranarak veriler toplanmıştır. Hemşire eğitimleri için eğitim birim kayıtları kullanılmıştır. İstatistiksel analiz olarak yüzde hesaplamaları kullanılmıştır.

Bulgular: Hastanemizde yatan toplam 3640 hastanın 1776'sı inme (%48,80) olarak saptanmıştır. Yatan akut inmeli hasta sayısı 1216 (%68,47) olarak bulunmuştur. Hastaların yattığı ortalama gün sayısı ise 27,6 gün olarak saptanmıştır. Hastaların demografik özelliklerine bakıldığında yatan hastaların 1005'i erkek (%56,59), 771'i kadın (%43,41) olup cinsiyete göre yaş ortalamasına bakıldığında erkek hastaların yaş ortalaması 64,18 olarak saptanırken kadın hastaların yaş ortalaması 68,78 olarak saptanmıştır. İnme risk faktörlerine bakıldığında hastanemizde yatan hastaların %59,74'ünde hipertansiyon (HT), %25,16'sında diyabetes mellitus (DM), %13,56'sında hiperlipidemi (HL), %15,03'ünde ise kardiyak hastalık,%6,41'inde üriner enfeksiyon, %3,71'inde pulmoner enfeksiyon, %0,5'inde derin ven trombozu, %0,56'sında ise malignite mevcuttur. Yatış esnasında bası yarası olan inmeli hasta sayısına bakıldığında 123 (%6,92) olarak tespit edilmiş olup, yatış sırasında yeni oluşan bir bası yarasına rastlanmamıştır. İnme tanısı almış bası yaralı hastaların hastanede yatan toplam bası yarası olan hasta sayısına oranına bakıldığında %32,97olarak bulunmuştur. Bası yarasına en sık rastlanan anatomik lokalizasyon sakrum 65 (%52,84) olurken, en az rastlanan lokalizasyon ise 1 hasta (%0,81) ile dirsek bölgesi olmuştur. Hemşirelere verilen bası yarası eğitimleri yılda 2 adet olup eğitime katılan hemşire oranı %71,5 olarak saptanmıştır. Refakatçilere verilen bası yarası eğitim sayısı yılda 12 adet olup eğitime katılım oranı %57,3 olmuştur.

Sonuç: İnme hastalarında bası yarası görülme oranı %6,92 olarak saptanmış olup, en sık lokalizasyon sakrum olarak bulunmuştur. Hastanede açılan yeni bası yarası oranının sıfır olması, rehabilitasyon hastanesinin bası yarası ile ilgili gerekli farkındalığın ve hemşire, refakatçi eğitim düzeyinin oluştuğunu göstermektedir.

Anahtar kelimeler: İnme, Bası yarası, Rehabilitasyon

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Introduction

Stroke is a brain vascular disease that affects millions of people in the world every year and causes disability [1]. Complications following a stroke are known to increase hospital stay and patient care costs [2]. European Pressure Ulcer Advisory Panel (EPUAP) defines pressure ulcer as; local injury to the skin and / or subcutaneous injury on the bone protrusion that occurs with pressure or friction with pressure [3]. The pressure ulcer, which occurs as a complication in stroke, has been reported at different rates in different patient populations. It was found to be 0.7% in 140 rehabilitation patients in Singapore, and 18% in a study of 607 patients with acute stroke hospitalized in Scotland after stroke [4,5].

In another study, patients with Barthel Index below 10 were included in the study and the rate of compression sores in stroke was found to be 22% [6]. When we search the education levels of the nurses about pressure ulcers there is a study that investigated the knowledge of intensive care nurses about pressure ulcer in Turkey, 78.8% of nurses reported that they had previously received training about pressure ulcer [7]. Although there have been few studies on pressure ulcers in stroke and information on pressure ulcers of health personnel; to the best of our knowledge, there is no study comparing the rates of pressure ulcer in stroke and in-service training of nurses in the literature. The aim of this study is to investigate the pressure ulcer rates of stroke patients in a public rehabilitation hospital and concurrent in-service training rates of nurses about pressure ulcers.

Materials and methods

This is an observational study. After obtaining permission from the hospital management for retrospective file scanning, the necessary information was collected from the hospital data in accordance with the Helsinki Declaration. For 3 years (01/01/2016-12/31/2018), the files of inpatient stroke patients in our hospital were retrospectively scanned and the data were collected. The demographic characteristics of the patients, whether they had acute (first 6 months) or chronic stroke during the hospitalization, mean number of days of hospitalization, accompanying pathologies, presence and localization of pressure ulcers during hospitalization, and whether new pressure ulcers developed during hospitalization were recorded. Hospital in-service training unit records were used for personnel training data of the nurses about pressure ulcers. To calculate the rate of nurses participating in training, the number of nurses receiving training on training day was divided by the number of nurses working actively in the hospital on the same day. The same ratio was calculated for the companions. For statistical analysis percentage calculations were used.

Results

Of the 3640 patients in our hospital, 1776 had stroke and 1216 of these patients had acute stroke (Table 1, 2). The average number of bedtime days for patients diagnosed with stroke was 27.6 days. The demographic characteristics of stroke patients are presented in Table 3 and the accompanying pathologies and rates are shown in Table 4. The number of stroke patients with pressure ulcers during hospitalization was 123 (6.92%) and no new pressure ulcers were found during hospitalization in the rehabilitation hospital. The ratio of the pressure ulcer patients diagnosed with stroke to the total number of hospitalized pressure ulcer patients was found to be 32.97% (Table 5). The most common anatomic localization of pressure ulcer was found to be in sacrum at 65 stroke patients (52.84%), while the least common localization was elbow with 1 patient (0.81%).

In-service training about pressure ulcers given to nurses was 2 times a year and the rate of nurses participating in the training was 71.5%. The number of education provided to the companions about pressure ulcers was 12 per year and participation rate was 57.3%.

Table 1: Stroke and non-stroke inpatient patients

	n	%
Stroke inpatient rehabilitation patients	1776	48.80
Non stroke inpatient rehabilitation patients	1864	51.20
Total	3640	100

Table 2: Acute and chronic stroke ratios

	Number of patients	
	n	%
Acute stroke	1216	68.47
Chronic stroke	560	31.53
Total	1776	100

Table 3: Patients ratios and average age according to gender

	Average age	n	%
Male	64.18 years	1005	56.59
Female	68.78 years	771	43.41
Total		1776	100%

Table 4: Rates of secondary diagnosis in stroke patients

	Patients	
	n	%
Hypertension	1061	59.74
Diabetes mellitus	447	25.16
Hyperlipidemia	241	13.56
Cardiac pathologies	267	15.03
Urinary tract infection	114	6.41
Kidney failure	32	1.80
Pulmonary infection	66	3.71
Deep venous thrombosis	9	0.50
Cancer	10	0.56

Table 5: Pressure ulcer ratios

Ratio of pressure ulcers in stroke patients		Ratio of pressure ulcer patients with stroke diagnosis to the all of patients with pressure ulcers		New pressure ulcers during hospitalization	
Patients	Ratio %	Patients	Ratio %	Patients	Ratio %
123	6.92	123	32.97	0	0

Discussion

Stroke is a major health problem that affects millions of people all over the world every year. In a study conducted in 195 countries all over the world; the second most important cause of Disability-Adjusted Life Year (DALY) is cerebrovascular diseases [1]. Stroke can occur across very different disease spectrum. Post-stroke hospitalization rates and the cost of the stroke patient to the health system may also vary depending on where the patient is in this wide range of stroke spectrum. It is known that pressure ulcers and similar complications that occur after a stroke increase both the duration of hospitalization and the cost of the disease [2]. When the rates of pressure ulcers after stroke are examined, very different results can be seen; these results vary from 0.7% to 22 % [4,5]. The most important reason for this variability is that the stroke patient profile taken into the study is different from each other and the facility where the study is performed. For example, in the study, where the rate of pressure ulcers in stroke was found to be 22%, study population was patients with a Barthel Index below 10 which means patient profile is more dependent [6]. In another study, stroke patients in

the intensive care unit were taken as a sample and pressure ulcer rate was 28% [8].

In our study, we evaluated 1776 patients with acute and chronic stroke who received inpatient treatment at the Rehabilitation Hospital. We did not use any functional status index as exclusion criteria and we found pressure ulcers in 123 stroke patients (6.92%).

Our data include both acute and chronic stroke cases and assess the rates of pressure ulcer in stroke regardless of all other functional characteristics of the patient.

In a study conducted in a stroke-specific hospital, it was shown that 22% of pressure ulcers found in stroke patients occurred during the hospitalization period [8]. In our study, no new pressure ulcer was detected in patients during their hospitalization period.

Reasons for the absence of new pressure ulcers can be considered as adequate repetitive training for both nurses and companions. Another factor is the fact that patients with active rehabilitation indications are hospitalized rather than unconscious palliative care patients because our hospital is a secondary branch hospital and don't have an intensive care unit.

The most common anatomic localization of pressure ulcers was sacrum, while the least common anatomic localization was the elbow. This data is consistent with current literature [8].

The ratio of nurses who received in-service training for pressure ulcer in the hospital was calculated as 71.5% .This ratio was calculated by dividing the number of nurses who received in-service pressure ulcer training to the number of nurses who were actively working at the hospital on the same day. This ratio does not appear to be low since the inpatient and outpatient clinic services continue while there is in-service training for nurses and there are fixed nurses in charge in these departments during the trainings.

In a study that evaluated the level of knowledge of nurses about pressure ulcers in a training research hospital, it was seen that 78.8% of the personnel who participated in the study had previously received training on the pressure ulcers [7]. Since our study is a retrospective study, the staff was not asked if they had received any training related to the pressure ulcer before, and the rate of nurses actively participating in the training was calculated on the day of training. This rate is expected to rise higher numbers if a questionnaire is prepared by taking into account the previous trainings of nurses about pressure ulcers. The same applies to companions. In our hospital, pressure ulcer trainings are given every month for companions; a companion who has already undergone training may not be able to attend the second training that falls within his or her hospitalization period, or the companion may be a companion who is professional and has already undergone training for pressure ulcers. Questionnaires which evaluate pressure ulcer information level that will be conducted to both companions and nurses in a future prospective study may help us to have more clear information on this issue.

Considering that the most important treatment for pressure ulcer is prevention, nurse and companion training is thought to be closely related to the lack of a newly opened pressure ulcers.

Limitations

The lack of pressure ulcer staging is the main limitation of the study. In subsequent studies, staging of pressure ulcers may give us more information about the status of the pressure ulcers during hospitalization. Our current prediction is that pressure ulcers have improved in this period due to the absence of new pressure ulcers during hospitalization.

Conclusion

The incidence of pressure ulcer was 6.92% in stroke patients and the most common localization was sacrum. The fact that the rate of the new pressure ulcer opened in the hospital is zero indicates that the necessary awareness and staff training level regarding the pressure ulcer of the rehabilitation hospital has been established.

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Family functioning and child behavioral problems with Duchenne/Becker muscular dystrophy: A cross-sectional study

Duchenne/Becker musküler distrofi tanılı olgularda aile işlevselliği ve davranış problemleri: Kesitsel bir çalışma

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Abstract

Aim: Duchenne/Becker muscular dystrophy (DBMD) in children is associated with emotional and behavioral problems and impairment at family functioning. The current study aimed to explicate family functioning and child behavioral problems with DBMD.

Methods: The study involved 28 child and adolescents with DBMD attending Dokuz Eylul University Medical Genetics and Child and Adolescent Psychiatry Outpatient Clinic from January 2019 to March 2019 and comprised 50 healthy control subjects. The participants who were evaluated with Kiddie-Sads-Present and Lifetime (K-SADS-PL) by blinded professionals completed a data form containing questions regarding sociodemographic and clinical features, Wechsler Intelligence Scale for Children-Revised (WISC-R) (for only DBMD cases), the Beck Depression Scale (BDS), State-Trait Anxiety Inventory (STAI), Parenteral Attitude Research Instrument (PARI), the Child Behavior Checklist (CBCL) and Family Assessment Device.

Results: Mothers of the children with DBMD demonstrated higher scores in Beck Depression Inventory and State-Trait Anxiety Inventory scales, which is associated with anxious and depressive states as compared with those from the control group but not statistically significant (P=0.888, P=0.584 and P=0.646, respectively). DBMD cases demonstrated significantly higher scores in most of the Child Behavior Checklist (activities, withdrawn/depressed, somatic complaints etc.), meaning that they have many problem areas affecting family functioning and the quality of life of the patient (P<0.001).

Conclusion: This study demonstrated that, for parents who have children with DBMD, DBMD had a negative effect on their lives, and their family relationships. However, further studies with larger sample sizes are required to reach stronger conclusions.

Keywords: Muscular dystrophy, Child behavioral problems, Family functioning

Öz

Amaç: Çocuklarda; Duchenne/Becker Musküler Distrofisi (DBMD) duygusal ve davranışsal problemlerle ve aile fonksiyonlarında ki bozulma ile ilişkilidir. Bu çalışma, aile işlevselliğini ve davranış sorunlarını, DBMD olan olgularda araştırmayı amaçlamaktadır.

Yöntemler: Çalışma; Ocak 2019 ve Mart 2019 tarihleri arasında Dokuz Eylül Üniversitesi Tıbbi Genetik ve Çocuk ve Ergen Psikiyatrisi Polikliniği'ne başvuran 28 DBMD tanılı çocuk ve ergen ile 50 sağlıklı kontrol olgusunu içermektedir. Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam Boyu Şekli-Türkçe (K-SADS-PL) ile araştırmacılar tarafından değerlendirilen katılımcılara; sosyodemografik ve klinik özellikler ile ilgili sorular içeren veri formu, Wechsler Çocuklar İçin Zeka Ölçeği (WISC-R) (sadece DBMD vakaları), Beck Depresyon Ölçeği (BDI), Durum ve Süreklilik Kaygı Envanteri (STAI), Ebeveyn Tutum Değerlendirme Ölçeği (PARI), Çocuk Davranış Kontrol Listesi (CBCL) ve Aile Değerlendirme Ölçeği uygulanmıştır.

Bulgular: DBMD'li çocukların anneleri, Beck Depresyon Envanteri ve Durum-Sürekli Kaygı Envanteri ölçeklerinde, kontrol grubundakilere göre endişeli ve depresif durumlarla ilişkili daha yüksek ancak istatistiksel olarak anlamlı olmayan puanlar saptanmıştır (sırasıyla P=0.888, P=0.584 ve P=0.646). DBMD vakaları, Çocuk Davranışları Kontrol Listesinin çoğunda (aktiviteler, çekingen / depresif, somatik şikayetler, vb.) anlamlı olarak daha yüksek puanlar göstermiştir; bu, ailelerin işleyişini ve hastanın yaşam kalitesini etkileyen birçok problem alanına sahip oldukları anlamına gelmektedir (P<0.001).

Sonuç: Bu çalışma, DBMD'li çocukları olan ebeveynler için DBMD'nin yaşamları ve aile ilişkileri üzerinde olumsuz bir etkisi olduğunu göstermiştir. Bununla birlikte, daha güçlü sonuçlara ulaşmak için daha büyük örneklem büyüklüğünde daha fazla çalışma yapılması gerekmektedir.

Anahtar kelimeler: Kas distrofisi, Çocukluk çağı davranış problemleri, Aile işlevselliği

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Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked allelic diseases caused by mutations in the dystrophin gene [1]. These diseases, also called dystrophinopathy, are the most common neuromuscular diseases of childhood. Muscular dystrophies are hereditary, progressive, skeletal muscle diseases with muscular degeneration and characterized by loss of power. The beginning of the clinical symptoms varies from neonatal period to late adulthood [2].

In the treatment, it is aimed to provide new cells in order to repair the dystrophy needed to stop muscle degeneration or to preserve the regenerative capacity of the muscle. Nowadays, dystrophin-based treatment strategies as well as dystrophin-independent treatment methods are underway. Biological factors (lack of dystrophin and isoforms, effects on brain development and function), social and emotional factors and treatments which not specified to Duchenne/Becker muscular dystrophy (DMBD) patients constitute part of psychosocial health.

Some studies have explored psychosocial aspects and the effect of parenting for a child with DBMD. Their findings suggested that these parents accommodate some psychologic arrangements like facing loss, experiencing separation and also have shown higher stress and poorer health-related quality of life [3-5]. Nereo et al. [4] describes DMD like as a 'complex chronic condition' with impacts on the family similar to both chronic and terminal illnesses. Psychological and social consequences caused by the chronic condition affects both the child and the family. It is imperative to consider the common relationship between parents and children in the family view. On the one hand, the health status of the child depends on the psychological state of the parent and on the other hand the functioning and health of the parent affect the health of the child. Childhood chronic diseases like DMBD; symptoms, causes, treatment methods, course, daily activity limitation, long-term effect varies. However, there are common factors that cause stress response in children and families in all chronic diseases [6]. Research has identified large-scale parental stressors associated with increased economic burden of parents of children with chronic diseases, frequent hospitalization of parents of children, examination appointments, family roles that change with disease, and emotional adjustment [7]. According to the family systems model, it shows that families affect the well-being of children and that the health status of children affects the functioning of the family. Therefore, low-level problematic behaviors are observed in children with chronic diseases in high-functioning families. In this bi-directional interaction, behavioral problems and treatment course of children, especially in diseases such as DBMD; should not be examined independently of the social environment and family dynamics. This is an important issue in deciding on interventions for children's functionality.

When assessing the severity and course of problem behaviors in parents with chronic diseases from parental perspective, it is also important to consider parents' approach to disease and problem solving skills.

This study aimed to evaluate between behavioral problems, family functioning and psychopathology of DBMD and among healthy controls. A secondary aim of this study is to see the effects of long-term stress of parents with DBMD children; investigate the effects of neurological conditions, physical therapy and special education on parent attitude skills.

Materials and methods

The clinical sample of this study consisted of children with a history of 35 DBMD cases who admitted to Dokuz Eylul University Medical Genetics and Child and Adolescent Psychiatry Outpatient Clinic from January 2019 to March 2019 after the ethics committee approval was obtained. The Dokuz Eylul University Ethics Committee approved the study (Date: January 18th, 2019, Number: 2019/01-192). Priori power analysis demonstrated that a sample size of 42 participants per group was required based on an 80% power to detect the middle effect size (0.05) making use of an independent samples t-test with a 0.05 two-tailed significance level. Required number of patients could not be reached due to study schedule. Seven cases for whom missing or erroneous entries in the data collection instruments were found were excluded from the study. As a result, the data of a total of 28 children and adolescents with DBMD were subjected to statistical analysis.

The children who were admitted to our pediatrics outpatient clinic by parents for causes such as headache, acute infections but did not meet any diagnostic criteria constitutes healthy control group.

After the children and parents who were included in the study were informed about the purpose and method of the research, written consent was obtained from both groups. The participants who were evaluated with Kiddie-Sads-Present and Lifetime (K-SADS-PL) by blinded professionals completed a data form containing questions regarding sociodemographic and clinical features, Wechsler Intelligence Scale for Children-Revised (WISC-R) (for only DBMD cases), the Beck Depression Scale (BDS), State-Trait Anxiety Inventory (STAI), Parenteral Attitude Research Instrument (PARI), the Child Behavior Checklist (CBCL) and Family Assessment Device.

Sociodemographic data form

It is an information form filled by the researchers to obtain information about age, gender, education, family type, socioeconomic level, home conditions, status of parents, and background and family history.

Parental Attitude Research Instrument (PARI)

It was developed by Schaefer and Bell [8] (Total 115 items and 5 sub-dimensions). The adaptation of the scale to Turkish was performed by Küçük [9]. In the reliability study, the test-retest correlation coefficient was found to be 0.58-0.88.

Family assessment device

The McMaster Model of Family Functioning (MMFF), which aims to evaluate family problem areas and family functions according to the perception of family members, has been used clinically in families with Epstein et al. [10], in the United States by the Psychiatry and Human Behavior Department of the Medical Faculty of the Brown Hospital and the Butler Hospital in the framework of the Family Research Program developed by the family of the functions of the family to determine what matters or cannot meet the family is a

measurement tool that identifies the problem areas. The validity and reliability study of the scale was conducted by Bulut [11].

Beck Depression Scale (BDS)

It is a self-report based scale commonly used in the clinic [12]. BDS is a short, multi-lingual scale that has been developed for use in primary health care.

State-Trait Anxiety Inventory (STAI)

The State Trait Anxiety Inventory was developed by Spielberger et al. [13] in 1970, and adapted by Öner [14] and Le Compte to Turkish society in 1985 and it is a Likert type scale that measures state and trait anxiety levels separately with 20 questions. High scores indicate high levels of anxiety, and low scores indicate low anxiety levels. The Spielberger State and Trait Anxiety Inventory was filled with self-report to determine the parents' own anxiety levels.

Child Behavior Checklist (CBCL)

The 6-18 age group evaluates the problem behaviors of children and young people in terms of information obtained from their parents or caregivers [15]. The scale consists of 118 problem items. There are also 20 items related to social competence. The problems seen in the last 6 months are rated as 0, 1 and 2 according to the frequency of occurrence and the items are grouped into various subscales. Test-retest reliability of the scale was 0.84 in the total problem and 0.88 in the internal consistency [16].

Statistical analysis

Differences in all study variables were analyzed using the Statistical Package for the Social Sciences (IBM, NY), version 22 for Windows. Before the statistical analysis was performed, it was checked whether the data met the assumptions of the parametric tests and the normal distribution and homogeneity of variance by using the Shapiro–Wilk test. Variables that don't show normal distribution were evaluated by appropriate not show normal distribution were evaluated by appropriate analysis. In the interpretation of the variables, descriptive statistical techniques and quantitative data analysis were used. Chi-square analysis was used to compare categorical variables between groups. The Pearson Correlation Test was used to determine the direction and level of correlation between the variables, and the results were indicated by "r" (correlation coefficient) and "P" value (significance level). P < 0.05 was considered statistically significant.

Results

Table 1 summarizes those main features of the participants and the identification of the clinical characteristics between groups. A total of 78 children and adolescents were included in the study, 28 in the DBMD group and 50 in the healthy control group. The mean age of the patient group was 8.11 (2.76) and the mean age of the control group was 8.66 (2.71). There was no statistically significant difference between the groups in terms of the mean age (P=0.942). Also, no differences were detected on sex, parental education level and employment status between groups (Table 1).

When the Family Assessment Scale (FAD), which was filled by the parents in both groups, was evaluated, a statistically significant difference was found between the two groups in all subscale scores of the FAD, except problem solving, communication, roles. As the score from the all subscale scores of the FAD subscales increases, the function area in question is thought to be problematic.

Mothers of the children with DBMD demonstrated higher scores in BDI and STAI scales, which is associated with anxious and depressive states as compared with those from the control group but not statistically significant (P=0.888, P=0.584 and P=0.646, respectively). Mothers of the children with DBMD demonstrated significantly lower scores in PARI 1 and PARI 2 subscales, which is related to democratic attitude and attitude of over-parenting (evaluation of the mother's forced child intervention, the child's dependence on parents and measures encouraging conversations and sharing ratio with parents) as compared with those from the control group (P=0.051 and P=0.012, respectively). No significant difference was found in the other subscales in which the score increase in the scale reflects negative parental attitudes.

The comparisons of children behavioral problem areas between the DBMD and healthy groups using the CBCL subscales are presented in Table 3.

Table 1: Sociodemographic data of the DBMD patients and control groups

	DBMD n = 28	Controls n = 50	***P*-values**
Age* (mean (SD))	8.11 (2.76)	8.66 (2.71)	0.942
Gender n (%)	Male 28 (100%)	Male 50(100%)	
Mother's mean age (mean (SD))	34.06 (3.82)	36.41 (5.82)	0.382
Maternal education n (%)			
< 8 years	12 (42.85%)	22 (44%)	0.542
> 8 years	16 57.15(%)	28 (56%)	
Employment status n (%)			
Homemaker	20 (42.85%)	35 (42.85%)	0.235
Worker	8 (42.85%)	15 (42.85%)	

DBMD: Duchenne/Becker Muscular Dystrophy, SD: Standard deviation, * P<0.05, ** P<0.01

Table 2: Depression and Anxiety status, attitudes, and family functioning of mothers in the DBMD patients and control groups

	DBMD n=28 mean (SD)	Controls n=50 mean (SD)	***P*-values**
BDI	11.66 (8.66)	10.82 (7.03)	0.888
STAI-1	42.21 (14.76)	39.04 (9.77)	0.584
STAI-2	43.64 (10.47)	42.54 (7.52)	0.646
PARI 1- Attitude of over-parenting	38.14 (10.30)	42.44 (8.95)	0.051
PARI 2- Democratic Attitude	26.57 (3.63)	28.80 (3.88)	*0.012
PARI 3- Attitude of hostility and rejection	28.57 (8.10)	28.08 (8.53)	0.904
PARI 4- Marital Discordance	13.85 (3.54)	14.72 (4.54)	0.410
PARI 5- Authoritarian attitude	32.57 (7.97)	33.68 (9.20)	0.639
FAD 1- Problem Solving	1.78 (0.64)	1.98 (0.63)	0.229
FAD 2- Communication	1.66 (0.50)	1.83 (0.55)	0.192
FAD 3- Roles	2.00 (0.29)	1.96 (0.43)	0.929
FAD 4- Affective Responsiveness	1.55 (0.69)	1.83 (0.62)	*0.012
FAD 5- Affective Involvement	2.26 (0.53)	1.98 (0.47)	*0.011
FAD 6- Behaviour Control	2.01 (0.37)	1.75 (0.43)	*0.003
FAD 7- General Functioning	1.48 (0.46)	1.84 (0.57)	*0.011

DBMD: Duchenne/Becker Muscular Dystrophy, BDI: Beck Depression Inventory, STAI: State–Trait Anxiety Inventory, PARI: Parental Attitude Research Instrument, FAD: Family Assessment Device, SD: Standard deviation, * P<0.05, ** P<0.01

Table 3: Depression and Anxiety status, attitudes, and family functioning of mothers in the DBMD patients and control groups

	DBMD n=28 mean (SD)	Controls n=50 mean (SD)	***P*-values**
CBCL Activities	43.85 (9.51)	33.92 (12.15)	**< 0.001
CBCL Social	41.00 (8.09)	44.56 (7.83)	0.070
CBCL School	45.46 (6.45)	50.38 (4.12)	**< 0.001
CBCL Withdrawal/Depression	60.21 (5.34)	54.14 (4.07)	**< 0.001
CBCL Somatic Complaints	63.32 (6.76)	57.16 (6.01)	**< 0.001
CBCL Anxious/Depressed	57.03 (5.50)	56.70 (5.91)	0.590
CBCL Social Problems	59.92 (6.29)	54.98 (3.85)	**< 0.001
CBCL Thought Problems	60.32 (6.42)	55.98 (5.45)	*< 0.05
CBCL Attention Problems	57.10 (5.37)	54.68 (4.96)	*< 0.05
CBCL Rule-Breaking	55.75 (5.94)	53.64 (4.02)	0.143
CBCL Aggressive	56.03 (3.27)	54.24 (4.75)	0.116
CBCL Total Competence	41.57 (10.77)	37.18 (9.34)	0.128
CBCL Internalizing Problems	60.28 (5.68)	55.28 (6.05)	*< 0.05
CBCL Externalizing Problems	55.32 (4.62)	51.08 (6.14)	*< 0.05
CBCL Total Problems	58.96 (4.59)	53.22 (5.37)	**< 0.001

DBMD: Duchenne/Becker Muscular Dystrophy, CBCL: Child Behavioral Checklist, SD: Standard deviation, * P<0.05, ** P<0.01

Discussion

DBMD is a chronic disease with progressive proximal muscle weakness, mental impairment, hypertrophy in calves, and increased connective tissue in the muscle. In DBMD patients, the initial symptoms are usually frequent falls, running or stair climbing, and in many patients, the findings occur before the age of five years [2]. The main finding of our study is that behavioral problems and family functioning are worse than healthy controls in people with DMBD.

The results obtained in the studies investigating the psychosocial effects of DBMD differed due to the variables such as the clinical and demographic characteristics of the evaluated patient group and the nature of the measurement tools used. In terms of behavioral problems in our sample, we found that children and adolescents with DBMD had significantly higher CBCL scores on subscales of somatic complaints, withdrawal/depression, thought problems, social problems and attention problems, and had higher CBCL total problems scores, externalizing/internalizing problems than the healthy group. There were no statistically significant differences between the two groups in terms of aggressive behavior, anxiety/depression, rule breaking and total competence subscales. These findings are inconsistent with those of Sienko et al. [17], who found that children with DMD had no significant difference among the groups including internalizing and externalizing behaviors. The other hand, Colombo et al. [18] evaluated 47 children with DMD who were not differentiated from their intellectual abilities and found 23.4% internalized problems. Duchenne cases have mood and mood disorders and aggressive behaviors. In a study using a scale in which behavioral problems were evaluated, it was found that the families of DMD patients scored more than 32% of the cut-off point [19]. When all these results are evaluated together with the data of our study; disabilities of DBMD cases; it may be associated with behavior problems.

Mothers with children with DBMD compared to mothers with healthy children; depression and state-trait anxiety inventory scores were found to be significantly higher. DBMD mothers; Psychological, social, economic problems and the most struggling people to solve the daily life of children with disabilities, low self-esteem and depressive symptoms are defined [20]. The severity of the depressive symptom in mothers and the higher levels of anxiety; It may be related to loneliness, emotional-physical-economic difficulties caused by chronic disease. Also, the emotional commitment of the mother, the loss of hope for the future, and the deterioration in the quality of life of mothers may have contributed to this result. In a study evaluating the parents of DBMD; depressive symptoms at 40% [21], in some studies; the presence of increased levels of depression and anxiety in parents with a child with chronic disease is consistent with the results of our study [22,23].

Data from this study, it was found that mothers of children diagnosed with DBMD had difficulties in mental health and impaired family functioning. Consistent with previously reported studies, it is reported that depressive mothers exhibit a more negative parenting attitude. The roles and duties of the parents who cannot cope with the stress experienced in the family can be confused and disruptions in family functionality may occur. Some studies suggested that mothers who perceived life events outside their control and experienced extreme parental stress were more inadequate in motherhood, had no control over the events, and the sense of stress caused by the motherhood role led the mother to think about not responding to her child's negative behaviors [24,25].

When the FAD data were analyzed, it was found that the scores of DBMD group in “Affective Responsiveness”, "General Functioning", “Affective Involvement” and “Behavior Control” subscales were found to be statistically significant compared to the control group; “Problem Solving”, “Communication” and “Roles” subscales were not found any difference between the control group. Behavioral control includes assessment of the discipline applied by the parents. The control is asked to be flexible, solid, free or irregular. Parents of children diagnosed with DBMD think that behavior problems of their children will not change or may start to over react. Children with DBMD may not be able to adequately control their emotions and behaviors and may impose impulsivity on parents, so parents may have difficulty with appropriate Affective Involvement and Affective Responsiveness skills.

In our study, it was found that mothers of children with DBMD diagnosis had more difficulty in terms of mental health compared to controls; It is an important finding that should be kept in mind during the treatment process for the mothers of children. As a result of family intervention, it has been determined that the difficulties of the relatives of the patients have decreased in the care and that they can cope with the stress positively, there are positive changes in the family functions, the patient's compliance with the medication and control appointments increases, and the problem solving skills develop.

There are some limitations of our study. The fact that the health institution in which the patients were enrolled was the last step hospital, so that this was not a field study, the severity of physical illnesses were not measured, the sample size was small and the patients were more resistant to the treatment might have affected the research results.

Conclusions

When the results of our study are considered, it can be said that chronic muscle diseases constitute a burden which goes far beyond the medical dimension of the event both in practice and psychiatric terms for the family. Family functioning and severity of the child's disease may vary with the cognitive strengthening of maternal mothers who cannot cope with stress and the change in maternal behavior. In the treatment of children with muscle disease, it is important to include the family in the treatment process and family interventions are important and effective for caregivers.

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Prevalence of influenza vaccination among health care workers and adverse effects after vaccination: A cross-sectional study

Sağlık personelinin grip aşısı yaptırma sıklığı ve aşı sonrası istenmeyen etkiler: Kesitsel bir çalışma

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Abstract

Aim: Influenza is an important public health problem for the whole world and the prevalence of influenza vaccination is low. The aim was to determine the prevalence of influenza vaccination and adverse effect after seasonal influenza and/or pandemic A (H1N1) influenza vaccination in health care workers (HCW) working in Ankara.

Methods: It is a cross-sectional study. In March-April 2010, 1611 HCW from Atatürk Hospital, Sami Ulus Hospital and 13 Primary Health Care centers have been reached and survey was conducted.

Results: 41.1% of HCW have had seasonal influenza vaccination and 26.1% of them had side effects. Most of HCW, who have not been vaccinated; reported the needlessness of vaccination and fear of side effect as explanation of reason for being not vaccinated. 46.6% of examined HCW had pandemic influenza vaccination. After pandemic influenza vaccination, any of side effects was seen in 66.4% of vaccinated HCW. Most of HCW, reported the needlessness of vaccination, fear of side effect, inability to vaccinate, debates and contradictions on the views, as explanation of reason for being not vaccinated.

Conclusion: As a result, vaccination percent are under expected. HCW, like every part of public, are affected from actual discussions. For health services being not affected from these conditions, HCW's knowledge should be renewed and updated.

Keywords: Health care workers, Influenza vaccine, Adverse event

Öz

Amaç: Grip tüm dünya için önemli bir halk sağlığı sorunudur ve grip aşısı yaptırma sıklığı her yerde düşüktür. Araştırmada, Ankara'da görev yapan bazı sağlık personelinde mevsimsel ve/veya pandemik A (H1N1) grip aşısı yaptırma ve aşı sonrası istenmeyen etkilerin görülme sıklıklarını saptamak amaçlanmıştır.

Yöntemler: Araştırma kesitsel bir çalışmadır. Mart-Nisan 2010 yılında, Ankara Atatürk Eğitim Araştırma Hastanesi, Sami Ulus Eğitim Araştırma Hastanesi ve Etimesgut Sağlık Grup Başkanlığı'na bağlı 13 sağlık ocağında yapılan çalışmada 1611 sağlık çalışanına ulaşılmış ve anket uygulanmıştır.

Bulgular: İncelenenlerin %41,1'i daha önce mevsimsel grip aşısı yaptırmış ve yaptıranların %26,1'inde yan etki görülmüştür. Aşıyı yaptırmayanların büyük çoğunluğu, gerek duymadığı ve aşının yan etkilerinden korktuğu için aşı yaptırmadığını ifade etmiştir. İncelenenlerin %46,6'sı pandemik grip aşısı yaptırmıştır. Pandemik grip aşısı sonrası, %66,4'ünde bir yan etki saptanmıştır. Pandemik grip aşısı yaptırmayanlar gerek duymadığı için, yan etki sebebiyle, aşıya güvenmediği için, gündemdeki tartışmalar ve çelişkiler yüzünden aşıyı yaptırmadıklarını belirtmişlerdir.

Sonuç: Sonuç olarak, aşılanma yüzdeleri beklenilenin altındadır. Sağlık çalışanları da toplumun tüm kesimleri gibi gündemdeki tartışmalardan etkilenmektedir. Sağlık hizmetlerinin bu durumdan etkilenmemesi için sağlık çalışanlarının bilgileri eğitimlerle yenilenmeli ve güncellenmelidir.

Anahtar kelimeler: Sağlık çalışanları, Grip aşısı, Yan etki

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Introduction

Infectious diseases have been, and continue to be, the greatest public health problem for centuries in all countries of the world [1]. Influenza, a disease caused by influenza virus, which has an important place among infectious diseases, is an infection that has existed on Earth for more than 2000 years and is characterized by causing outbreaks rather than its clinical presentation [2].

Every year, 10-20% of the world's population is known to be infected with the influenza virus [2]. Its mortality rate is approximately 6-8% annually [3]. The annual costs of these patients range from 1-3 billion dollars [4]. Considering the population of Turkey, it is estimated that there are approximately 50,000 hospitalizations and 9,000 deaths in our country [5]. Today, more frequent but less effective pandemics are observed [6]. Pandemics have been observed every 10-50 years since the 16th century, causing millions of deaths, social detachment and economic losses [7].

2009 pandemic H1N1 influenza A virus is not the same as pandemic influenza viruses seen in 1918 and 1976 [8]. While it is more contagious and lethal compared to seasonal influenza, it is less lethal than previous pandemic influenza viruses [9]. The first case was observed in Mexico in April 2009 [10]. The disease began to spread rapidly, and the World Health Organization (WHO) announced in June 2009 that it was the Phase 6 pandemic [11].

As of April 2010, there have been reported cases of confirmed pandemic influenza H1N1 causing more than 17,853 deaths in more than 214 countries worldwide [12]. In our country, 627 deaths have been reported since April 2010 [13]. The first death in our country has been reported in a health worker. In our country, the outbreak occurred late, but there were more deaths than in European countries [14].

Influenza vaccines, which are among the strategies for prevention and control of influenza outbreak during the pandemic process, started to be used in the mid-20th century and are being developed every year [15,16]. There are limited studies on the frequency of influenza vaccination in societies, and the frequency is not known [15]. There is also no clear data on the percentage of seasonal influenza vaccination in our country. In limited studies, the most common cause of non-vaccination is reported to be the possible side effects [17]. In September 2009, the Pandemic H1N1 vaccine was introduced [18]. Effectiveness of the live attenuated vaccine is 85%, while effectiveness of the inactivated vaccine is 76%. Vaccination rates in both Turkey and some European countries are far below the desired level [17].

The H1N1 vaccine caused 25 vaccine-related deaths due to Guillain-Barre Syndrome in 1976 [19]. In October-November 2009 period, 82 adverse effects were reported in 1 million people who received H1N1 vaccine in the USA, while this figure was determined to be 47 in those who received seasonal flu vaccine with the same frequency [20].

In the period in which this study was conducted, a limited number of studies were published about the percentage of people receiving the pandemic flu vaccine and the side effects observed in healthcare personnel in Turkey and in other countries. Extensive studies are needed to respond to vaccine safety concerns, to prevent these concerns from affecting other vaccines within immunization programs, and to respond effectively to future outbreaks. The present study is one of the first comprehensive studies on these subjects.

The aim of this study was to determine the frequency of seasonal and/or pandemic A (H1N1) influenza vaccination among healthcare personnel in Ankara and the frequency of some adverse effects that may be seen after administration.

Materials and methods

This research is a cross-sectional study. A questionnaire was prepared for influenza / seasonal influenza vaccine and its side effects. In order to carry out the research, permission was obtained from the Ethics Committee of Atatürk Training and Research Hospital, Ankara Provincial Health Directorate and all three institutions where the research was conducted. The sample of the study consist 2034 health care workers working in Ankara Atatürk Training and Research Hospital (AEAH), Ankara Dr. Sami Ulus Maternity and Children's Health / Diseases Training and Research Hospital (SUEAH) and Ankara Etimesgut Health Group Presidency (Primary Health Centers). It was aimed to reach the entire health care workers. A total of 1611 people were reached, which corresponds to 79.2% of the health care workers. The percentage of transportation is 75.4% for AEAH, 85.8% for SUEAH and 77.2% for primary health centers, respectively. Physicians, dentists, nurses, midwives, medical assistants, emergency medical technicians (EMT), x-ray technicians, lab technicians, medical technologists, dieticians and medical secretaries were included in the research.

Statistical analysis

For statistical analysis, descriptive statistics, Chi-Square, Fisher exact test and McNemar Test were used. In all analyses, the statistical significance level was accepted as 0.05. Odds Ratio (OR) and 95% Confidence Interval (CI) calculations were made in Epi Info Version 3.5.1. computer software.

Results

Table 1 shows the descriptive characteristics of the participants. The vast majority of those surveyed were female in the 25-34 age group and doctors.

Table 1: Distribution of descriptive properties of the investigations, Ankara, 2010

Descriptive properties (n=1611)	AEAH		SUEAH		Primary health centers		Total	
	n	%*	n	%*	n	%*	n	%*
Age								
≤24	169	20.2	93	15.6	32	18.1	294	18.2
25-29	200	23.9	163	27.3	26	14.7	389	24.1
30-34	215	25.7	133	22.3	21	11.9	369	22.9
35-39	108	12.9	64	10.7	46	26.0	218	13.5
40-44	89	10.6	80	13.4	29	16.4	198	12.3
≥45	56	6.7	64	10.7	23	13.0	143	8.9
Gender								
Female	527	63.0	446	74.7	136	76.8	1109	68.8
Male	310	37.0	151	25.3	41	23.2	502	31.2
Job								
Doctor	527	63.0	234	39.2	51	28.8	812	50.4
Dentist	9	1.1	4	0.7	6	3.4	19	1.2
Nurse	198	23.7	249	41.7	58	32.8	505	31.3
Midwife	29	3.5	50	8.4	42	23.7	121	7.5
Health officer	13	1.6	10	1.7	5	2.8	28	1.7
Laboratory assistant	15	1.8	11	1.8	9	5.1	35	2.2
Emergency medical technician	13	1.6	15	2.5	2	1.1	30	1.9
Other#	33	3.9	24	4.0	4	2.3	61	3.8
Chronical disease								
No	738	88.2	524	87.8	134	75.7	1396	86.7
Yes	99	11.8	73	12.2	43	24.3	215	13.3
Food / Drug allergies								
No	785	93.8	543	91.0	164	92.7	1492	92.6
Yes	52	6.2	54	9.0	13	7.3	119	7.4

* Column percentage, # Other: Radiology technician, medical technologist, dietitian, AEAH: Atatürk Training and Research Hospital, SUEAH: Sami Ulus Training and Research Hospital

Table 2 shows the status of receiving seasonal / pandemic influenza vaccines of the participants. 36.0% (238 people) of the health care workers who had previously received the seasonal flu vaccine do not intend to receive the vaccine next year.

69.9% of all health personnel in the study stated that they did not consider getting the pandemic influenza vaccine from the first moment, while 53.4% stated that they did not get it. The majority of those who received the pandemic influenza vaccine got the vaccine in the first weeks of November, when the campaign began.

Of 949 health care workers who did not get the seasonal influenza vaccination previously, 29.7% stated that they did not need vaccination, 8.1% feared side effects, 6.6% did not experience flu disease frequently and 6.4% did not trust in the vaccine. 26.2% stated that there was no reason for not receiving vaccination.

Table 3 shows distribution of the reasons for not receiving vaccination. The participants did not receive the pandemic influenza vaccine mostly because they did not need it and were afraid of the side effects. One in every ten people do not trust the vaccine.

According to table 4; young people, primary care physicians, laborants/medical assistants, and those who had previously received seasonal influenza vaccination and had no side effects received pandemic influenza vaccine more than others.

According to table 5, 26.1% of participants had some side effects after the seasonal influenza vaccine and 66.4% had some side effects after the pandemic influenza vaccine. Side effects are non-serious side effects.

Table 2: The status of receiving seasonal influenza and pandemic influenza vaccines of the participants, Ankara, 2010

(n=1611)	n	% *
The status of participants' receiving seasonal influenza vaccine previously		
Not vaccinated	949	58.9
Vaccinated	662	41.1
The status of participants' receiving seasonal influenza vaccine this season		
Not vaccinated	1024	63.6
Vaccinated	587	36.4
The status of participants' consideration of receiving seasonal influenza vaccine next year		
Does not intend to get vaccinated	1047	65.0
Considers getting vaccinated	564	35.0
Participants' consideration of receiving pandemic influenza vaccine from the first time		
Did not consider (getting influenza vaccination)	1126	69.9
Considered (getting influenza vaccination)	485	30.1
The status of participants' receiving pandemic influenza vaccine		
Not vaccinated	861	53.4
Vaccinated	750	46.6

* column percentage

Table 3: Distribution of the reasons for not receiving vaccination of those who did not get pandemic influenza vaccine among the surveyed, Ankara, 2010

Reasons for not receiving pandemic influenza vaccine (n=861)	n	%*
Does not need to get vaccinated	188	22.5
Afraid of side effects	98	11.8
Does not trust in the vaccine	88	10.5
Thinks that there is not enough information about the vaccine	62	7.4
Thinks that it can be protected by natural methods	48	5.7
Does not believe that the vaccine is effective	30	3.6
Because of receiving negative feedback from those who have been vaccinated	35	4.2
Because of having the disease already	22	2.5
Because the vaccine is used for the first time	18	2.1
Does not believe in the H1N1 virus	18	2.0
Thinks that there is a commercial purpose	11	1.3
Does not want to be a subject	10	1.2

* Percentage of columns taken based on the number of people

Table 4: The status of participants' receiving pandemic influenza vaccine according to some of their descriptive characteristics, Ankara, 2010

Descriptive properties (n=1611)	The status of participants' receiving Pandemic influenza vaccine: Not vaccinated n	%	Vaccinated n	%	OR	CI 95%
Age						
≤24	232	78.9	62	21.1	1	-
25-29	183	47.0	206	53.0	4.2	2.9-6.0
30-34	192	52.0	177	48.0	3.4	2.4-4.9
35-39	85	39.0	133	61.0	5.8	3.8-8.8
40-44	94	47.5	104	52.5	4.1	2.7-6.2
≥45	75	52.4	68	47.6	3.3	2.1-5.3
χ^2= 105.5 P=0.001						
Job						
Doctor	419	51.6	393	48.4	1	-
Dentist	11	57.9	8	42.1	0.7	0.2-2.1
Nurse	298	59.0	207	41.0	0.7	0.5-0.9
Midwife	60	49.6	61	50.4	1.0	0.7-1.6
Health officer	6	21.4	22	78.6	3.9	1.4-10.8
Laboratory assistant	3	8.6	32	91.4	11.3	3.3-46.9
Emergency medical Technician	24	80.0	6	20.0	0.2	0.2-0.7
Other#	40	65.6	21	34.4	0.5	0.3-1.0
χ^2= 59.19 P=0.001						
Departments						
Internal Sciences	436	48.9	455	51.1	2.0	1.6-2.6
Surgical Sciences	352	66.4	178	33.6	1	-
Dental Clinic	7	53.8	6	46.2	1.7	0.5-5.7
Primary health centers	66	37.3	111	62.7	3.3	2.3-4.8
χ^2= 61.6 P=0.001						
The status of participants' receiving seasonal influenza vaccine previously						
Not vaccinated	623	65.6	326	34.4	1	-
Vaccinated	238	36.0	424	64.0	3.4	2.7-4.2
X^2= * P=0.001						
Side effect occurrence after seasonal influenza vaccine (n=662)						
No	188	38.4	301	61.6	1.5	1.4-2.9
Yes	50	28.9	123	71.1	1	-
χ^2=* P=0.012						

* Fisher exact test

Table 5: Occurrence of side effects after seasonal/pandemic influenza vaccine, Ankara, 2010

	n	% *
Occurrence of side effects after receiving seasonal influenza vaccine previously, Ankara, 2010 (n=662)		
Observed	489	73.9
Not observed	173	26.1
Occurrence of side effects after seasonal influenza vaccination this season (n=587)		
Observed	419	71.3
Not observed	168	28.7
Occurrence of side effects after pandemic influenza vaccination (n=750)		
Observed	252	33.6
Not observed	498	66.4

* column percentage

Figure 1 and 2 show side effects of vaccines. After the seasonal and pandemic influenza vaccine, influenza-like diseases were the most common. Additionally, non-severe side effects such as local pain, fever, muscle pain and headache were observed. Only the presence of food/drug allergy and gender affected the occurrence of side effects after the pandemic influenza vaccine. More side effects were observed in females and those with food/drug allergies as expected.

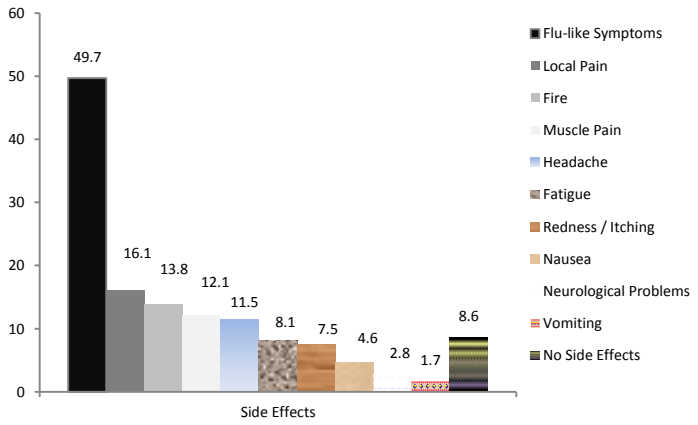

Figure 1: Distribution of side effects after pandemic influenza vaccine in the participants, Ankara, 2010

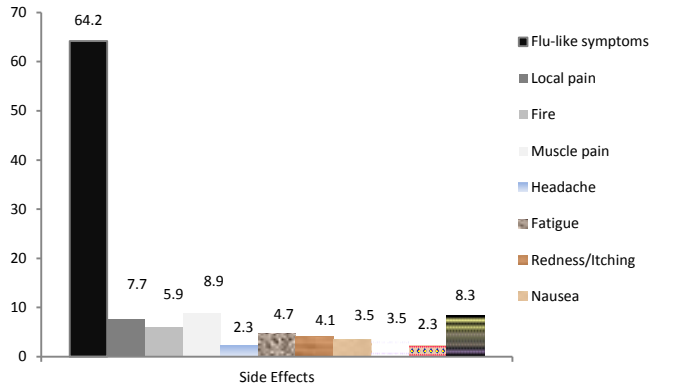

Figure 2: Distribution of side effects of seasonal influenza vaccine previously received by the participants, Ankara, 2010

Discussion

The prevalence of vaccination in health workers was reported to be 14-48% in different studies conducted in different countries [21,22]. In our country, on the other hand, the prevalence of seasonal influenza vaccination among health personnel varies between 1.1-48.6% [23,24]. Higher rate of vaccination found in the present study may be due to the fact that influenza vaccine has been on the agenda for the last few years and that institutions have started to provide free vaccination for their staff. The reasons for not getting vaccinated are consistent with many studies in the literature. As expected, those with chronic diseases received seasonal influenza vaccines more than those without chronic diseases. In the present study, it was determined that the least vaccinated group in the 2010 season was the group working in surgical units. 58.2% of primary health care workers received the seasonal influenza vaccine, which is 3.2 times higher than those working in surgical units. Primary care workers are more sensitive to preventive services, and preventive services are better provided in these organizations.

In the study, only 30.1% of health workers considered getting the pandemic influenza vaccine from the first moment. This percentage is expected as the frequency of seasonal influenza vaccination is low among health workers. On the other hand, the controversial claims about vaccines and the fact that there has been an ongoing debate about them for a long time may have influenced health workers to get a pandemic influenza vaccine. Danielle Ofri's article describes how lots of people who asked when the vaccine would be available in the early days of the pandemic later refused to receive it because of the current debate [25]. The highest percentage of people getting the pandemic influenza vaccine in all studies is in Mexico. As this was the starting point of the pandemic, it was an expected finding that health workers wanted to take precautions and approved the vaccine.

When asked about the reason for not getting the pandemic influenza vaccine, about one-fifth (22.5%) said they did not get the vaccine because they did not need it, 11.8% said they did not get the vaccine because of the side effect, 10.5% said they did not trust in the vaccine, and 3.3% said they did not get the vaccine because the prime minister did not. 22.2 percent did not specify the reason for not receiving it. The media may also be considered to be effective again in not getting the pandemic flu vaccine, as the controversial debates on the agenda raised doubts about the vaccine. The reason why 185 people did not specify a reason may be due to the fact they were hesitant because the issue was mediatic and political and because they did not tell the actual reasons for not receiving the vaccination.

It was found that gender did not affect the status of receiving the pandemic influenza vaccine. In studies conducted in the Netherlands, Frankfurt and Istanbul, unlike this study, it was found that male health care workers received a significantly higher rate of pandemic influenza vaccine than female health care workers [21].

As expected, those who had previously received a seasonal influenza vaccine received a pandemic influenza vaccine 3.4 times more than those who did not; those who intended to be vaccinated next year received a pandemic influenza vaccine 5.1 times more than those who did not; and those who received a seasonal influenza vaccine this season received a pandemic influenza vaccine 6.3 times more than those who did not. Similarly, those who received seasonal influenza vaccines in Canada in the previous year received pandemic influenza vaccines 6 times more [26]. In studies conducted in Istanbul, Greece and the Netherlands, similarly, the percentage of pandemic influenza vaccination was significantly higher among those who had previously received seasonal influenza vaccination [21]. In another study conducted by general practitioners in France, previous seasonal influenza vaccination was found to be the most important independent predictive factor for receiving pandemic influenza vaccines [27].

In this study, one out of every five people who had previously received a seasonal influenza vaccine had side effects. Side effects are the expected mild side effects. In the US, the incidence of side effects after the 2010 seasonal influenza vaccine was estimated as 47 per 1 million [20]. In this study, when asked what the side effects were, approximately two-thirds said that they had flu-like symptoms.

According to our study, one out of every three people who received a pandemic flu vaccine had side effects. Side effects were mild side effects that could disappear in a few days. In the study conducted in China, no serious side effects were detected, and 12-50% local side effects and 16-49% systemic side effects (fever, etc.) were detected [28]. In a study conducted in Australia, 56.3% of the vaccinated individuals had local side effects and 53.8% had systemic side effects after the vaccination. Most commonly, pain at the injection site, headache and listlessness were observed [29]. In an article published in the USA, it was reported that 21.5 cases of GBS, 5.75 sudden deaths, 86.3 optic neuritis in women and spontaneous miscarriage in 397 million women would be detected if 10 million people were examined to identify the side effects of the pandemic influenza vaccine [30].

There was a great difficulty experienced in persuading the health personnel to complete the questionnaire during the research. Limitations of the study are not to reach all health care workers and not to observe long-term side effects of vaccination.

Conclusion

Based on these results, it was concluded that health personnel approached the seasonal/pandemic influenza vaccines with suspicion, that they were not sure whether vaccines were safe and were affected by the debates in the media. In order to be more cautious and conscious, and to ensure that this

contradictory situation does not affect other routine vaccinations in the event of an outbreak in the following years.

Health personnel can be trained according to their level on influenza virus transmission, diagnosis, treatment and strategies to be implemented in unvaccinated individuals and their consequences and responsibilities for patients and themselves. The state should have sanctions on mass-media and prevent the making of news that will lead to panic. In order to have more confidence in vaccines, the production of vaccines can be initiated in our country under the full public assurance. In the interventions aimed at the community such as prevention of epidemic and protection by vaccination, primary health care institutions that are within the society and which are the easiest to access should be given importance.

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Carotid intima-media thickness and cardiac functions in children with neurofibromatosis type 1

Nörofibromatozis tip 1 tanılı çocuklarda karotis intima-media kalınlığı ve kalp fonksiyonları

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Abstract

Aim: Neurofibromatosis type 1 is a multisystem disorder, affecting primarily the skin, nervous and musculoskeletal systems. Various cardiovascular abnormalities, ranging from congenital heart disease to vasculopathy and hypertension are main clinical features of cardiovascular involvement. The aim of this study was to evaluate cardiac functions and carotid intima-media thickness by conventional and tissue Doppler echocardiography in terms of vasculopathy and cardiac involvement in children with neurofibromatosis type 1.

Methods: A cross-sectional study is designed with 36 Neurofibromatosis patients (20 boy and 16 girl) as study group, with a mean age of 9.7(3.5) years with 36 healthy controls (18 males and 18 females) with a mean age of 10.3 (2.2) years. Instant blood pressures were measured. Conventional and tissue Doppler echocardiography were performed. Carotid intima-media thickness, left ventricular ejection fraction and left ventricular fractional shortening were measured with M mode. Mitral early (E), late (A) flow velocities were measured by pulsed-wave Doppler, mitral early (E), late (A) flow velocities ratio was calculated. Tissue Doppler echocardiography was performed from the lateral annular junction of mitral valve and left ventricular myocardial performance index (Tei) index was calculated. Early diastolic flow (E') velocity was measured with tissue Doppler echocardiography.

Results: Left ventricular systolic functions were normal in both groups. Mitral early flow velocities were lower (P<0.001) in the study group. Also Mitral early / late velocities ratio was significantly lower (P=0.004) and mitral early flow velocity/ tissue Doppler early diastolic flow velocity ratio was higher (P=0.045) in the study group. The left ventricular Tei index was calculated as 0.42 (0.1) in the study group and 0.39 (0.1) in the healthy controls (P=0.03). The mean of carotid intima-media thickness was 0.46 (0.01) in the study group and 0.44 (0.01) in the control group (P=0.002). Systolic blood pressures were higher in the study group (P=0.04).

Conclusion: Tei index and diastolic flow velocities in mitral valve support the left ventricle diastolic dysfunction in children with neurofibromatosis type 1. Carotid intima-media thickness suggests vasculopathy and early effects of hypertension due to neurofibromatosis type 1.

Keywords: Neurofibromatosis, Carotid intima-media thickness, Heart

Öz

Amaç: Nörofibromatozis tip 1 öncelikle deri, sinir sistemi ve kas iskelet sistemini tutan multisistemik bir hastalıktır. Doğumsal kalp hastalıklarından vaskülopati, hipertansiyona kadar çeşitlilik gösteren kardiyovasküler tutulum olabilir. Nörofibromatozis tip 1 tanılı çocuklarda vaskülopati ve kardiyak etkilenme açısından konvansiyonel ve doku Doppler ekokardiyografi ile kalp fonksiyonlarının ve karotis intima media kalınlığının değerlendirilmesi amaçlandı.

Yöntemler: Nörofibromatozis tip 1 tanısı alan 36 hasta (20 erkek, 16 kız), 9,7 (3,5) yıl ve yaşları 10,3 (2,2) yıl olan 36 sağlıklı kontrol ile kesitsel çalışma yapıldı. Kan basınçları ölçülerek kaydedildi. Konvansiyonel ve doku Doppler ekokardiyografiyi uygulandı. M mod ile karotis intima media kalınlığı, sol ventrikül ejeksiyon fraksiyonu, sol ventrikül kısalma fraksiyonu ölçüldü. Diastolik mitral erken akım (E) ve mitral geç akım (A) velositeleri Doppler ile ölçüldü, mitral erken akım / geç akım oranı hesaplandı. Mitral kapak lateral anüler bileşkeden doku Doppler ekokardiyografi yapıldı, myokardiyal performans indeksi (Tei) hesaplandı. Doku Doppler ile mitral erken diyastolik akım velositesi (E') ölçüldü.

Bulgular: Sol ventrikül sistolik fonksiyonları tüm hastalarda ve kontrollerde normaldi. Çalışma grubunda erken mitral akım velositeleri daha düşüktü (P<0,001). Çalışma grubunda mitral erken akım / geç akım oranı anlamlı olarak daha düşük (P=0,01), mitral erken akım/ doku Doppler mitral erken diyastolik akım oranı sağlıklı kontrollere göre daha yüksekti (P=0,04). Sol ventrikül Tei indeksi çalışma grubunda 0,42 (0,1) ve sağlıklı kontrol grubunda 0,39 (0,1) olarak hesaplandı (P=0,03). Karotis intima media kalınlığı çalışma grubunda 0,46 (0,01), sağlıklı kontrol grubunda 0,44 (0,01) idi (P=0,002). Çalışma grubunda sistolik kan basınçları anlamlı olarak daha yüksek saptandı (P=0,04).

Sonuç: Tei indeksi ve mitral kapaktaki diyastolik akım velositeleri Nörofibromatozis tanılı çocuklarda diyastolik disfonksiyonun başladığını göstermektedir. Karotis intima media kalınlığı nörofibromatozise bağlı vaskülopatiyi ve hipertansiyonun erken belirtisini düşündürmektedir.

Anahtar kelimeler: Nörofibromatozis, Karotis intima media kalınlığı, Kalp

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with an incidence of approximately 1:3000 [1,2]. NF1 is characterized by its cutaneous manifestations, café-au-lait spots, lentigines, and neurofibromas with a variable clinical expression. Individuals with neurofibromatosis type 1 can develop various cardiovascular abnormalities, ranging from congenital heart disease to vasculopathy and hypertension [3]. Neurofibromatosis type 1 - related vasculopathy includes renal and cerebral artery stenosis, aortic coarctation and arteriovenous malformations [4]. Most individuals with NF1 vasculopathy are asymptomatic, which may contribute to underestimation of its frequency. Because of the potential pathogenetic significance of NF1-associated cardiovascular alterations, we aimed to evaluate the prevalence of cardiac and vascular involvement with M-mode, 2-dimensional echocardiography and tissue Doppler scan in children with NF1.

Materials and methods

Study population

This cross-sectional study was conducted between October 2011 and August 2014. Thirty-six children who referred to the Pediatric Cardiology outpatient clinic at the Kayseri Education and Research Hospital (Kayseri, Turkey) with the diagnosis of Neurofibromatosis type 1 were accepted as study group. The healthy control group consisted of 36 healthy children (18 boy and 18 girl) who were referred to the Pediatric Cardiology clinic for innocent murmur but had normal cardiac evaluation. The mean age of the study group were 10 years (range: 4-19 years). The diagnosis of NF1 was on the basis of the guidelines developed in the 1987 National Institutes of Health Consensus Development Conference Statement [5]. Written informed consent to participate in the study was obtained from the caregiver or the individual as appropriate.

Blood pressure (BP) was measured with a standard mercury sphygmomanometer after the subjects were allowed to rest for 5 minutes. Complete 2-dimensional echocardiograms and Doppler scan studies were obtained with Vingmed System 7 (Vivid 7, GE, Horten, Norway) with 3 MHz probes. Left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF) were measured on M-mode echocardiography. Diastolic mitral inflow velocity was measured with pulsed-wave Doppler echocardiography in the apical four-chamber view. Early (E) and late (A) diastolic mitral peak velocities together with E/A ratios were calculated. All study participants were examined with tissue Doppler echocardiography (TDE). At least three cardiac cycles were recorded. The velocity curves were taken from the base of the mitral annulus at the insertion of the mitral leaflets in left ventricle free wall at the standard apical four-chamber view. Myocardial performance index or Tei index was calculated from the sum of the isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for global left ventricular function [6]. Mitral valve early diastolic tissue Doppler velocity (E') was. Mitral E/E' ratios were calculated. Carotid images were taken while the patients were in supine position with a cervical angulation of 30° towards the contralateral side. Measurements were performed at a level including an area of 1 cm at the most distal part of the right and left main common carotid arteries, at the carotid bifurcation, and at an area 2 cm from the most proximal part of the internal carotid arteries. Carotid intima-media thickness (CIMT) measurements were obtained longitudinally at the distance between the vessel lumen echogenicity and the media/adventitia echogenicity using the M mode.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS software (Version 16.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normally distributed (Kolmogorov-Smirnov test or Shapira-Wilk), they were described as mean (standard deviation). Comparisons between groups were applied using Mann–Whitney U test were used for the data which is not normally distributed. While investigating the associations between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. Values of $P<0.05$ were considered statistically significant.

Results

We included 36 NF1 patients (16 girl, 20 boy) for study group and 36 healthy children (18 girl, 18 boy) for control group. The mean age was 9.7(3.5) years (minimum: 5, maximum: 18) in the study group and 10.3(2.2) years (minimum: 6, maximum: 17 years) in the control group. No significant difference was detected between the study group and the healthy controls with regard to gender and age. There were 9 NF1 patients with electroencephalographic abnormalities and taking antiepileptic drugs. Twenty-six NF1 patients have pathognomonic findings on cranial magnetic resonance imaging. Optic glioma was detected in two patients. Mild-to- moderate mitral valve insufficiency due to mitral valve prolapsus was detected in four patients. Left ventricular hypertrophy was detected in one patient with plexiform neurofibroma. The instant blood pressures were summarized in Table 1.

Table 1: Instant blood pressures of study and control group

Blood pressure	Study group Mean (SD) (min-max)	Control group Mean (SD) (min-max)	*P*-value
TA systolic (mmHg)	128 (18) (110-140)	118 (13) (100-130)	0.04
TA diastolic (mmHg)	69 (14) (55-85)	66 (11) (60-85)	0.09

TA: Blood pressure, SD: Standard deviation

Systolic blood pressures of study group were statistically higher than those of the healthy controls ($P=0.04$). Left ventricle systolic functions obtained from conventional echocardiography (LVFS and LVEF) were compared, and no significant differences were detected between the study group and the healthy controls. The study group showed a significantly lower early mitral peak velocities (E) with respect to healthy controls ($P<0.001$). There was a statistically significant ($P=0.004$) lower Doppler ratio of early to late transmitral flow velocity in the study group when compared with controls. Mitral E/E' ratios were statistically significant low in the study group ($P=0.045$). Tei indices of the study group were 0.42 (0.1) (minimum: 0.36, maximum: 0.51) and it was higher when compared with healthy controls [0.39 (0.1) (minimum: 0.31, maximum: 0.43)] ($P=0.03$). CIMTs were measured as 0.46

(0.01) in the study group and 0.44 (0.01) in the control group; measurement values were statistically higher in the study group (P=0.002) (Table 2) (Figure 1).

Table 2: Echocardiography results of study and control group

	Study group Mean (SD)	Control group Mean (SD)	*P*-value
Mitral E (m/s)	0.94 (0.02)	1.08 (0.02)	<0.001
Mitral A (m/s)	0.7 (0.02)	0.7 (0.01)	0.11
Mitral E/A	1.34 (0.06)	1.54 (0.05)	0.004
Mitral E/E'	6.6 (0.2)	6.1 (0.1)	0.045
LV Tei Index	0.42 (0.1)	0.39 (0.1)	0.03
Carotid Intima-Media Thickness (mm)	0.46 (0.01)	0.44 (0.01)	0.002

SD: Standard deviation

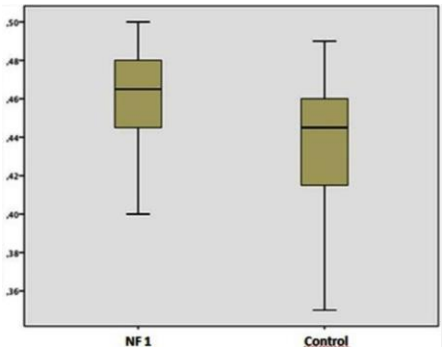

Figure 1: Carotis intima-media thickness of study group and healthy control

Discussion

Cardiac events and arrest due to vasculopathy are known pathologies in NF1 patients. Vasculopathy usually affects the arterial system, leading to cerebrovascular (e.g., narrowed or ectatic vessels, vascular stenosis, aneurysm, or moyamoya disease) or renal artery disease [4]. Left ventricular hypertrophy, mitral valve prolapsus and valve insufficiency, coarctation of aorta, and pulmonary valve stenosis have been reported in NF1 patients [7]. In this study, four patients had mild to moderate mitral valve deficiency due to mitral valve prolapsus. Systolic heart functions were similar between the study group and control group. There were significant differences in the diastolic Doppler velocities of study group when compared with the healthy controls. The exact mechanism of diastolic dysfunction should be explained with higher systolic blood pressures in the study group.

Tedesco and colleagues reported a shorter isovolumic relaxation time in NF1 patients than in controls [8]. In the current study, NF1 patients showed significantly lower early mitral peak velocities (E) with respect to controls, which reflects an impairment of the early (passive) phase of diastole requiring high energy consumption, namely active performance (relaxation) of the left ventricle. In addition, there was a lower Doppler ratio of early to late transmitral flow velocity, thus highlighting the predominant impairment of diastolic cardiac function.

It must be known that such pulsed-wave Doppler measurements are affected by multiple hemodynamic factors such as preload and heart rate variability. Tissue Doppler echocardiography measurements and Tei index are less affected from such factors. Tei indices were statistically higher in the study group, which reflects diastolic heart dysfunction with preserved systolic function.

CIMT is considered as a reflection of multiple risk factors; however, primary contributors to intima-media thickening are age and hypertension. The presence of hypertension significantly increases CIMT values due to hypertrophy of the media layer of the vessel wall. Baroncini et al. [9] reported that CIMT was higher in hypertensive children and adolescents when compared to the control groups. Hypertension is a risk factor for intima-media thickening. In the current study systolic blood pressures were higher in the study group but just one patient with plexiform neurofibroma had hypertension and left ventricular hypertrophy. Xu et al. [10] reported an in vivo model of NF1 obstructive vascular disease and have shown that Nf1 regulation of Ras plays a critical role in vascular smooth muscle proliferation after injury. Intimal thicknesses of the carotid artery, renal artery, aorta, and main branches should be measured for early diagnosis of NF1-related vascular disease and neointimal proliferation.

Our study has some limitations: First, although normal CIMT values based on age were identified for adults, a standard range according to age is unknown for pediatric populations. As no studies have been conducted on this topic thus far, it is not possible for us to draw a definitive conclusion on which CIMT values can be considered as abnormal in the pediatric age group. Until the standardization of CIMT values is achieved for children, researchers should perform comparisons with control groups that include healthy children or perform individual measurements regularly. Second, diastolic heart functions should be affected by multiple cardiovascular factors such as hypertension and vasculopathy. Heart functions should be checked regularly for prevention of dysfunction.

Conclusion

Tei index and diastolic flow velocities in mitral valve support the left ventricle diastolic dysfunction in children with neurofibromatosis type 1. Tei index is a more sensitive and precise method for evaluation of systolic and diastolic functions. CIMT monitoring should be useful for vasculopathy detection in NF1 patients.

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia associated with bronchiectasis: A rare case

Bronşektazi zemininde gelişen diffüz idiyopatik pulmoner nöroendokrin hücre hiperplazisi: Nadir rastlanan bir olgu

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Abstract
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is the precursor neuroendocrine tumor proliferations comprising extended focal extraluminal nodules in whole lung occasionally or limited to the bronchial or bronchiolar walls. A 30-year old patient who underwent lower left lobectomy due to the extended saccular bronchiectasis was presented. Histopathological examination of the surgical specimen revealed diffuse idiopathic pulmonary neuroendocrine cell hyperplasia associated with bronchiectasis.
Keywords: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, Bronchiectasis, Surgery

Öz
Nöroendokrin hücre hiperplazisi çoğunlukla havayolu mukozasında bazal membranı penetre etmeyecek şekilde ortaya çıkan nadiren tüm akciğerde yaygın odaksal ekstralüminal nodül oluşturan nöroendokrin tümör öncülü proliferasyonlardır. Bu çalışmada 30 yaşında, genişletilmiş sakküler bronşektazi nedeniyle opere edilen ve cerrahi spesmenin histopatolojik değerlendirmesinde ek olarak diffüz idiyopatik pulmoner nöroendokrin hücre hiperplazisi saptanan olgu sunuldu.
Anahtar kelimeler: Diffüz idiyopatik pulmoner nöroendokrin hücre hiperplazisi, Bronşektazi, Cerrahi

Introduction

There are numerous neuroendocrine cells within the bronchial and bronchiolar epithelium of normal lung tissue. A reactive neuroendocrine cell proliferation is observed in chronic pulmonary inflammation. Neuroendocrine cell hyperplasia is commonly seen without penetrating the basement membrane of the airway mucosal. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) are the precursor neuroendocrine tumor proliferations comprising extended focal extraluminal nodules in whole lung occasionally or limited to the bronchial or bronchiolar walls [1]. Neuroendocrine cell hyperplasia and tumorlets are frequently detected in the surrounding scar tissues and bronchiectasis and emphysematous areas, and during the microscopic examination of surgical specimens or autopsy materials.

In this report, a male diagnosed with DIPNECH associated with bronchiectasis in his histopathological examination of surgical specimen and who underwent surgery due to bronchiectasis, was presented.

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Case presentation

While a 30-year-old male with a history of smoking 15 packs of cigarette/year and obesity (Body mass index: 30 kg/m^2) and not having any additional systemic disease was assessed in a center, he was transferred to us as an extended saccular bronchiectasis in the lower left lobe of his lung was detected on computed tomography of the thorax.

He did not complain of flushing, hypertensive attack, tachycardia and diarrhea. Surgical operation was planned through the complaint of hemoptysis and extended saccular bronchiectasis. Extended bronchiectasis was detected in the lower left lobe during the surgery and lower left lobectomy was performed. Mediastinal lymph node dissection was not added as malignity was not considered.

Pathology results revealed one nodular tumor with a diameter of 3 mm on the specimen of extended saccular bronchiectasis obtained by lower left lobectomy material. DIPNECH was detected in consequence of lam revision performed at the out-center hospital. No CD56+, Chromogranin A, Synaptophysin + Ki-67 5% Mitosis were found in the pathological examination (Figure 1).

The decision of applying chemotherapy or radiotherapy were not taken during the council of thoracic oncology and only follow-up was recommended. Our case was followed-up for 17 months without any complaint.

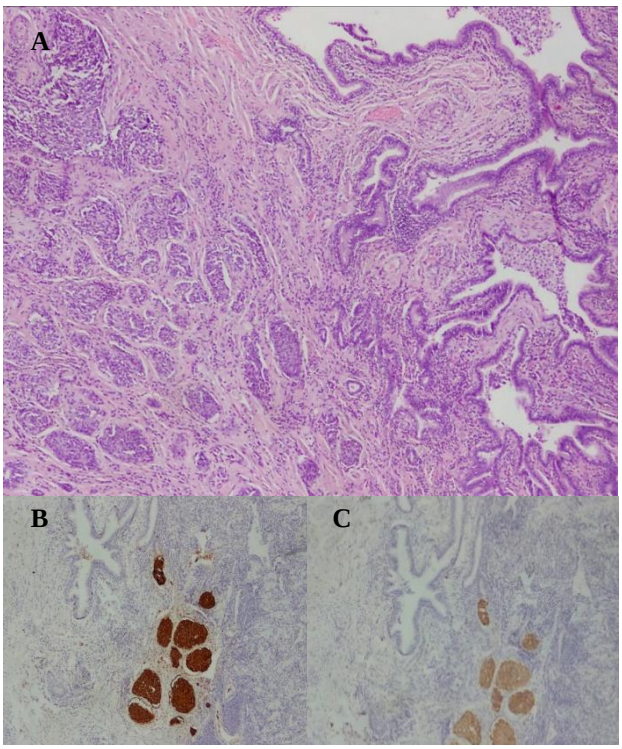

Figure 1: A: Neuroendocrine cells in small groups as well as bronchial structures. Neuroendocrine determinants are positive in the immunohistochemical study of Chromogranine (B) and Synaptophysizine (C).

Discussion

DIPNECH is a rare clinicopathological condition. Pulmonary neuroendocrine cell hyperplasia is defined as an adaptive response to chronic hypoxia in smokers or in subjects living at high altitudes [1].

Pulmonary tumorlets are defined as nodular proliferation of organoid pattern in bronchioles and originated from Kulchitsky cells. They are accidentally seen in the damaged lungs due to chronic apses, granulomatous inflammation, emphysema, infarction or similar chronic disease associated with bronchiectasis or other pulmonary sequestrations. It has been asserted that carcinoid tumorlets might be developed as a secondary response to hypoxic stress in the pathologies of bronchiectasis and sequestration [2].

It should be considered that pulmonary tumorlets must be examined as pulmonary neuroendocrine tumors and they might show intraepithelial neoplastic transformation to carcinoid. Therefore, although the primary reason of pulmonary tumorlet is benign, these patients must be followed-up for lymphatic metastasis as in patients with carcinoid [3].

Tumorlet and peripheral carcinoid are rarely associated with metastasis and lymphoid invasion. Of the typical carcinoid tumors, 4-11% tend to metastasis to the lymph nodes [4,5]. Tumorlets were classified as benign preinvasive lesions in the histopathological classification of World Health Organization (WHO) [6]. So ever, tumorlets are accepted as benign tumors, there are cases with metastasis to the lymph nodes [7,8].

The association of bronchiectasis, tumorlet and DIPNECH, which was detected in our case as well, might also trigger premalignant lesions, except the common complications, such as hemoptysis due to bronchiectasis and recurrent infections. Therefore, it should be kept in mind that early surgical therapy will prevent recurrent symptoms and further malignancies by detecting premalignant tumors at the onset of disease, in bronchiectasis patients not responding to medical therapy.

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Treatment of allopurinol-induced toxic epidermal necrolysis with high dose corticosteroids and intravenous immunoglobulins

Allopurinol nedenli toksik epidermal nekrolizin yüksek doz kortikosteroidler ve intravenöz immünoglobulinler ile tedavisi

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Abstract

Toxic epidermal necrolysis (TEN) is an uncommon, acute and severe adverse reaction triggered by drugs, infections and malignancies. Drugs are the main cause of the disease. The most common drugs are sulfonamides and penicillins and the most often associated infectious agent is herpes simplex virus. Allopurinol is the first line drug for serum lowering therapy in gout and is approved by the US Food and Drug Administration (FDA). In recent studies, allopurinol was found to be the most commonly associated drug causing life-threatening drug reactions. Here, we aimed to present a rare case of TEN induced by allopurinol, the efficacy/harm of high dose systemic corticosteroids and use of intravenous immunoglobulins (IVIg) in the treatment of TEN.

Keywords: Toxic epidermal necrolysis, SCORTEN, Allopurinol, IVIg, Methylprednisolone

Öz

Toksik epidermal nekroliz (TEN), ilaçlar, enfeksiyonlar ve maligniteler tarafından tetiklenen nadir, akut ve ciddi bir advers reaksiyondur. İlaçlar hastalığın ana nedenidir. En yaygın ilaçlar sulfonamidler ve penisilinlerdir ve en sık ilişkili bulaşıcı ajan herpes simplex virüsüdür. Allopurinol, gutta serum düşürücü tedavi için ilk sıra ilaçtır ve ABD Gıda ve İlaç İdaresi (FDA) tarafından onaylanmaktadır. Son araştırmalarda, allopurinolün yaşamı tehdit edici ilaç reaksiyonlarına neden olan en yaygın ilişkili ilaç olduğu bulundu. Burada, allopurinolün neden olduğu nadir bir TEN vakası, TEN'in tedavisinde intravenöz immünoglobulinlerin kullanımı (IVIg) ve yüksek doz sistemik kortikosteroidlerin etkinliğini/zararlarını sunmayı amaçladık.

Anahtar kelimeler: Toksik epidermal nekroliz, SCORTEN, Allopurinol, IVIg, Metilprednizolon

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Introduction

Toxic epidermal necrolysis (TEN) is an uncommon, acute and severe adverse reaction which is characterized by necrosis of the epidermis [1]. Its incidence is approximately one per million a year and mortality rate is approximately 40% [2,3]. TEN is considered by a hypersensitivity reaction and triggered by drugs, infections and malignancies. The most common drugs are allopurinol, antibiotics, anticonvulsants, non-steroid anti-inflammatory drugs [1]. It is characterized by a rapidly progress which usually starts with a form of maculopapular rash, followed by atypical, targetoid erythematous or purpuric macules and bullous lesions on the skin. It can be accompanied by systemic symptoms and mucosal involvement. Fever, mild elevation of hepatic enzymes, intestinal and pulmonary manifestations can be seen [4]. A score called SCORTEN developed by Bastuji-Garin et al. [5] determines the variables as predictors of prognosis and risk of death in patients with TEN. Systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, antitumor necrosis factor drugs are the treatment options [6].

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Case presentation

A written consent was obtained from the patient before taking pictures and for using. An 85-year-old man patient initially noted the appearance of maculopapular rash and pruritus on his body. Over the next following 3 days, bullous lesions and exfoliation was started. He had a history of allopurinol taking before two weeks. Dermatological examination showed maculopapular rash in the extremities (Figure 1), diffuse erythema and exfoliation on the trunk (Figure 2) and scalp, large bullous lesions on the palmoplantar region (Figure 3). Oral and genital mucosa had erosion according to the seconder candida infection (Figure 4). He had atrial fibrillation, benign prostatic hyperplasia, hypertension, chronic renal failure and cerebrovascular accident as additional diseases. Histopathology showed subepidermal blister with confluent, full-thickness necrosis of the blister roof, reveals necrosis in all layers of the epidermis caused by apoptosis of keratinocytes and the dermis displays minimum inflammatory changes (Figure 5). SCORTEN score was 4. IVIg from 2gr/kg and methylprednisolone from 1mg/kg/day was started to the patient. IVIg doses divided into five consecutive days. Methylprednisolone was given for 24 days. After the treatment, the skin and mucosa findings completely healed. But pneumonia developed during treatment which may be caused by high doses of steroid. The drug reaction was resolved but he died from septic shock and pneumonia.

Figure 1: Maculopapular rash on the legs

Figure 2: Maculopapular rash on the trunk

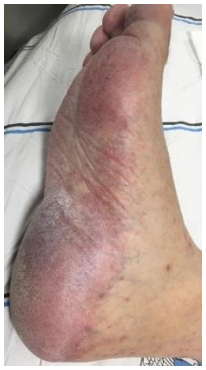

Figure 3: Large bullous lesion on the plantar region

Figure 4: Erosions and hemorrhagic cruts in the oral mucosa

Discussion

TEN is a rare and serious reaction to life-threatening. The pathogenesis of the disorder is still unknown. Genetic sensitivity, antigen-specific immunity and the synthesis of mediators of cell death are thought to play a role in the development of the disease. It is considered as a T cell mediated type IV hypersensitivity disorder [7]. The necrosis occurs in kerophytocytes due to the death of keratinocytes with apoptosis. The binding of Fas (CD95), a membrane receptor present in keratinocytes, with its FasL ligand (CD95L), and the release of the perforin and granzyme B pathways are leading to apoptosis [1].

The drugs, infections and malignancies can play a role in the etiology. The 80% of TEN cases depend on drugs. Allopurinol is one of the most common drug in the development [1,8]. In our case, the disease was attached to allopurinol, too. It is commonly used in gouty arthritis and uric acid nephropathy to lower uric acid. However, allopurinol causes cutaneous adverse drug reactions. One study [8] reported a strong association of HLA-B*58: 01 with allopurinol-induced cutaneous adverse drug reactions.

SCORTEN score is used for disease prognosis [5]. It determines the probability of death. It is determined according to age, pulse rate, neoplasia status, body surface area, blood urea nitrogen, glucose, and bicarbonate levels [9]. The score was 4 in our patient.

Patients with TEN should preferably be treated in burn units. The first care should include supportive and symptomatic measures: body temperature control, hydration and electrolyte replacement, special attention to the airways, preventing secondary infection, pain control, maintenance of venous access distant from the affected areas, early oral nutrition or parenteral nutrition, if necessary, and anticoagulation [10]. Systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, anti-tumor necrosis factor drugs and N-acetylcysteine can be used in the treatment of skin lesions. Systemic corticosteroids were previously noted the treatment of choice, however there have been conflicting evidence with reported increased rates of infection, prolonged hospitalization and higher rates of mortality, while other studies have found some benefit [11]. In recent times, there have been numerous studies [12-14] that have supported the effectiveness and safety of IVIg. IVIg contains anti-Fas antibodies that inhibit the Fas/Fas ligand (FasL) interaction [6]. We used a combination of high dose systemic corticosteroids and IVIg because of higher age of patient and SCORTEN 4 in our case according to the study results.

In conclusions, we aimed to present this rare case because of draw attention to caution in terms of severe drug reactions when starting allopurinol and the efficacy/harm of high dose systemic corticosteroids and use of IVIg in the treatment of TEN.

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Case report
Olgu sunumu

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Biphasic synovial sarcoma: A rare cause of axillary mass

Aksiller kitlenin nadir bir nedeni; Bifazik sinovyal sarkom

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Abstract

Synovial sarcoma is a subtype of soft tissue sarcoma which mostly affects the lower extremities, especially in young adults. Axillary involvement of the synovial sarcoma is a rarely seen clinical condition. A 68-year-old female applied with a rapidly grown palpable 4x4cm conglomerated mass in her right axilla. Except for the palpable axillary mass, her physical examination was regular. She was scanned for any distant metastasis with thoracoabdominal computerized tomography and breast ultrasonography with mammography. Tru-cut biopsy was performed on the palpable conglomerated axillary mass, and the pathological examination of the tru-cut biopsy specimen was reported as biphasic malignancy. In order to obtain a detailed examination and definite diagnosis, the mass was dissected and resected from axilla with extensive resection. Postoperative pathological examination was reported as a biphasic SS, and the surgical margins were clear. During the post-operative period, the patient had adjuvant chemoradiotherapy. There was no tumor relapse, both clinically and radiologically fourteen months after the surgery. Elder patients presenting with axillary lymphadenopathy, atypical, rare synovial sarcoma should be kept in mind. Total surgical excision should be performed, and clear margins should be obtained for the treatment of localized synovial sarcoma of the axilla.

Keywords: Synovial sarcoma, Lymphadenopathy, Breast cancer

Öz

Sinovyal sarkom sıklıkla genç erişkinlerde görülen, alt ekstremiteleri etkileyen bir yumuşak doku sarkomudur. Sinovyal sarkomun aksilla tutulumu çok nadir görülen bir klinik durumdur. 68 yaşında kadın hasta sağ aksillada ele gelen, hızlı büyüyen, konglomere, yaklaşık 4x4 cm çapında kitle yakınması ile başvurdu. Yapılan fizik muayenesinde aksiller kitle dışında ek bir özellik yoktu. Hasta torako-abdominal bilgisayarlı tomografi, meme ultasonu ve mammografi ile metastaz ve primer odak açısından araştırıldı. Tru cut biyopsi ile palpabl aksiller kitleden örnekleme yapıldı. Patolojisi bifazik malign kitle uyumlu gelen hastaya tanısal amaçlı eksizyonel biyospi yapıldı. Kitle sağlam cerrahi sınırlarla eksize edildi. Postoperatif kitle patolojisi bifazik sinovyal sarkom olarak raporlandı. Hastaya postoperatif adjuvant kemo-radyoterapi verildi. İzlem 14. ayında olan hastada klinik, radyolojik olarak nüks saptanmadı. Aksiller lenfadenopati ile başvuran ileri yaşta hastalarda sinovyal sarkom akılda tutulmalı, tedavisinde sağlam cerrahi sınırla eksizyon yapılmalıdır.

Anahtar kelimeler: Sinovyal sarkom, Lenfadenopati, Meme kanseri

Introduction

Synovial sarcoma (SS) is a rarely seen subtype of soft tissue tumor which has epithelial and mesenchymal differentiation [1]. SS typically affects the extremities and mostly seen in adolescents and young adults and consists of 8% of the soft tissue tumors [1]. Histologically, there are three subtypes of SS; monophasic, biphasic and poor differentiated. Most frequently seen subtype in adults is the monophasic type. SS is most commonly seen as a painless, palpable mass without radiological or clinical diagnostic features [2]. There was no consensus about the management of this disease, but most patients undergo surgical excision aiming to have clean surgical margins and the consequent adjuvant radiotherapy [1-4].

In this paper, we aimed to present biphasic SS of the axilla in an elderly female patient.

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Case presentation

A 68-year-old female applied with a rapidly growing indolent palpable mass for two months. She had no history of chronic disease, family history on malignancy, or drug use. Except 4× 4 cm conglomerate mass in her right axilla, her physical examination was unremarkable. Mammography was performed, but there were no significant findings. Superficial tissue ultrasonography was performed; a lesion consistent with cystic, solid mass was found in the right axillary with a diameter of 4 cm (Figure 1). A suspicious appearance was reported in terms of metastasis. For axillary lymphadenopathy, the most frequent possible differential diagnosis is breast cancer. In order to exclude the possibility, ultrasonography and mammography were performed. Mammography reported a well-defined, hypoechoic BI-RADS 4 malignant solid lesion with hyper-echogenic inter-septal occurrences with millimetric cystic areas in the right axilla 46x32 mm in size. Thoraco-abdominal computerized tomography scan showed no evidence of metastasis, except the 4x4 cm axillary mass (Figure 2). Tru-cut biopsy was performed, and the pathological examination revealed biphasic malignancy, which included epithelial and mesenchymal cells, which was not a leading result. Therefore; for definitive diagnosis, total surgical excision was performed, and clean surgical margins were obtained. The patient did not have postoperative complications. The postoperative histopathological examination was compatible with biphasic type synovial sarcoma (Figure 3, 4).

Postoperatively, the patient received adjuvant chemoradiotherapy. Either clinically or radiologically, no tumor relapse was observed 14 months after surgery,

Written informed consent was obtained from the patient for treatment, surgery and publication.

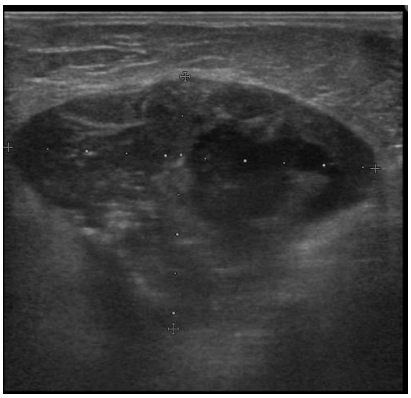

Figure 1: Superficial tissue ultrasonography shows; A lesion consistent with necrotic lymphadenopathy in the right axillary lobule with a diameter of 4 cm

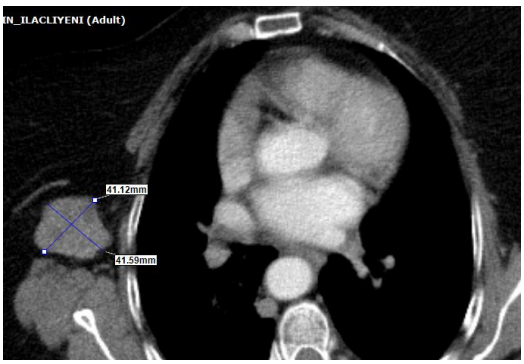

Figure 2: Thorax computerized tomography scan showed a 4x4 cm measured mass which localized right axillary region

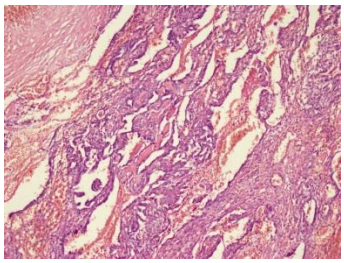

Figure 3: Biphasic synovial sarcoma H&E x100

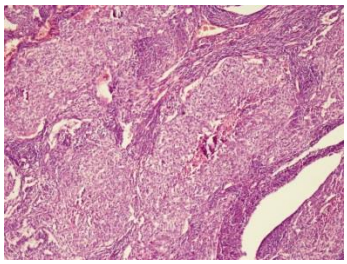

Figure 4: Epithelioid and spindle cell areas H&E x100

Discussion

SS is a rarely seen subtype of soft tissue tumor which has epithelial and mesenchymal differentiation [1]. Mostly presents between the ages of 15 and 40 years [4], but our patient was out of this age range. The most common tumor localization is the lower extremity, especially around the knee area. Upper extremities are rarely affected. In the studies conducted on malignant soft tissue tumors [1,2], 6-8% were reported as SS. But, in literature, only five cases of SS were reported to be located in the axillary region [5].

Prognosis of synovial sarcoma is mostly poor, and the 5-year and 10-years survival rates change between 38-76% and 20-63% respectively [6]. Prognostic features of synovial sarcoma are the size of the tumor, high-grade histology, surgical margin positivity, and metastases at the time of diagnosis. In addition to that, the prognosis is worse in elderly patients [3].

Removal of the tumor with clear surgical margins is vital in the prognosis and essential in preventing local recurrence. Studies are indicating that preoperative neoadjuvant chemoradiotherapy should be given in synovial sarcoma treatment according to grade, size, and localization and consequently, performing surgery and giving postoperative adjuvant chemotherapy treatment have a positive contribution on survival [1].

The treatment strategy of synovial sarcoma is multidisciplinary. Patients undergo surgical resection, which is combined with adjuvant/neoadjuvant radiotherapy. However, in advanced tumors, a combination of surgery, radiotherapy, and chemotherapy is given. Among the soft-tissue tumors; synovial sarcoma is more chemo-sensitive compared to the other types. However, for adult synovial sarcoma, the use of chemotherapeutic agents is controversial. Tyrosine kinases receptor, interferon alfa, radio-immuno-therapeutic agents, AKT-mTOR pathway drugs are being examined for the treatment of SS [7].

Herein we reported an elderly female patient who had an axillary mass due to synovial sarcoma, which was diagnosed with surgical resection.

In conclusion, patients presenting with axillary mass, atypical, rare synovial sarcoma should be considered. Biphasic synovial sarcoma of the axilla is a rare type with unclear pathogenesis, and the number of studies is limited. With more extensive case series, a better understanding of pathogenesis and management of this disease may be better addressed.

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Thymic mucoepidermoid carcinoma: A case report

Timik mukoepidermoid karsinoma: Olgu sunumu

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Abstract
Mucoepidermoid carcinoma of the thymus is a rare malignant neoplasm of the anterior mediastinum. There are less than 30 cases described in the English literature. We report a case of a 77-year- old man with right chest pain. Thorax CT scan showed a lobulated cystic mass having a focal solid portion with direct invasion of the adjacent pericardium in the anterior mediastinum. He underwent surgical resection for his anterior mediastinal mass via right thoracoscopic surgery without any complication. He had an uneventful recovery and was discharged on the sixth postoperative day.
Keywords: Thymus, Mucoepiderdoid carcinoma, Mediastinum

Öz
Timik mukoepidermoid karsinoma, anterior mediastende izlenen nadir bir malignitedir. Literatürde açıklanan 30'dan az vaka mevcuttur. Bizim olgumuz; sağ göğüs ağrısı olan, toraks BT'de anterior mediastende komşu perikardın direkt invazyonu ile fokal bir solid kısma sahip lobüle kistik kitle tespit edilen 77 yaşında bir erkek hastaydı. Anterior mediastinal kitlesi için herhangi bir komplikasyon olmaksızın sağ torakoskopik cerrahi ile rezeksiyon uygulandı. Sorunsuz bir iyileşme sürecinden sonra postoperatif altıncı günde taburcu edildi.
Anahtar kelimeler: Timus, Mukokepiderdoid karsinoma, Mediastinum

Introduction

Mucoepidermoid carcinoma is a rare tumor of the lung, which arises from the minor salivary glands in the tracheo-bronchial tree. Thymic carcinomas are unusual malignant neoplasms that have wide variety of morphologic appearances. Mucoepidermoid carcinomas of the thymus are extremely rare malignant mediastinal neoplasms and account for 2% of thymic carcinomas [1,2]. We report a case of mucoepidermoid carcinoma of the thymus with radiologic and histologic findings.

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Case presentation

In this case, a 77-year-old male, admitted to our hospital complaining of right chest pain was reported. The physical examination and laboratory studies were unremarkable. A 50x40 mm-sized lobulated cystic mass with focal heterogeneously solid portion in the anterior mediastinum was observed with thorax computed tomography (CT) scan of the chest (Figure 1). The patient did not show a mass with typical manifestations of myasthenia gravis. He had not ptosis and progressive muscle weakness. On thorax CT images, tumor was observed to adhere to the pericardium and infiltrated it (Figure 2). Neither pericardial/pleural effusion nor enlarged lymph nodes were detected.

Thorax CT guided fine needle biopsy of the anterior mediastinal mass was not performed. Thymectomy and resection of the adherent tissues were performed with the right video-thoracoscopic surgery. There were no intraoperative complications. Grossly, resected tumor measured 5x4 cm in size. It was a solid gray-red well-circumscribed mass with cystic compartments. Under the microscopical examination, mucous lake surrounded with atypical squamous epithelium and cylindric mucinous epithelium was seen in the thymus (Figure 3). Tumor has low mitotic activity without necrosis. Immunohistochemically, the epidermoid cells of the tumor were positive to pan-CK and p63 (Figure 4). The mucus-secreting cells are demonstrated by staining with mucicarmine (Figure 5). This part of tumor was diagnosed as low-grade mucoepidermoid carcinoma of the thymus according to the histopathological criteria of WHO classification [3].

Postoperative period was uneventful. Chemotherapy and radiotherapy of the main tumor bed were performed on the patient. Since there was a possibility of tumor metastasis to another anatomical location, the patient was referred to a whole body positron emission tomography positron emission tomography–computed tomography (PET-CT) study to search for the potentially secondary tumor, but there was not observed any abnormality. The fiberoptic bronchoscopy did not identify. Endobronchial lesion is located in tracheobronchial tree. So, the sign of the mucoepidermoid carcinoma of the lung was not detected. The patient was on regular follow-up for 4 months after discharging from hospital. He had remained asymptomatic, and there was no evidence of tumor recurrence during the period of postoperative follow-up. Informed patient consent was obtained for all procedures.

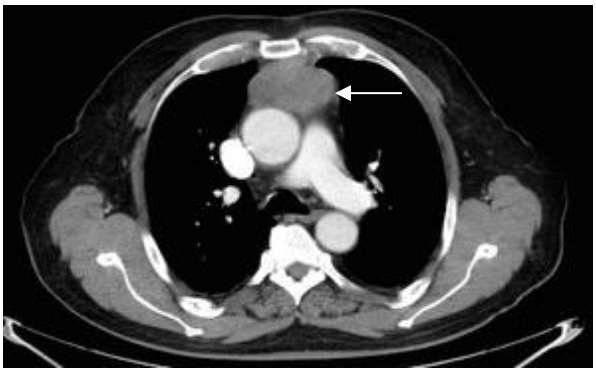

Figure 1: Computed tomography image of the patient showing a well-defined anterior mediastinal mass (arrow) within the thymus area

Figure 2: Computed tomography image of the patient showing the mass (arrow) in contact with the pericardium

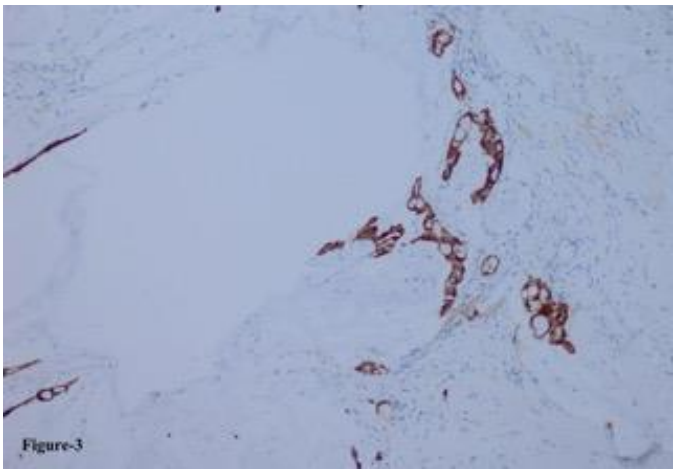

Figure 3: Mucous lake surrounding by atypical cylindric mucous epithelium and focal squamous epithelium (HE stain: x200)

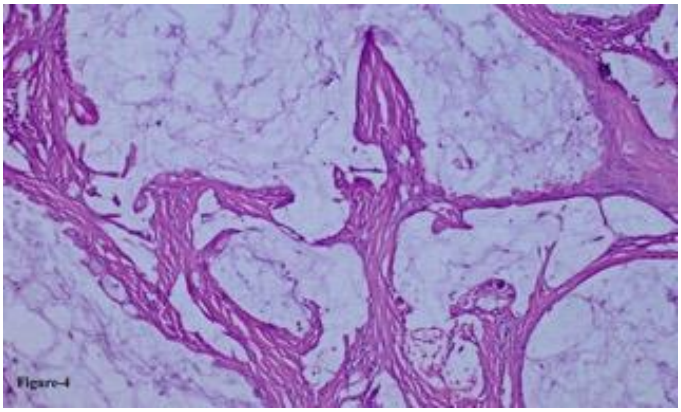

Figure 4: Atypical epithelial cells with pan-CK (+) staining surrounding mucous lake. (pan-CK stain: x200)

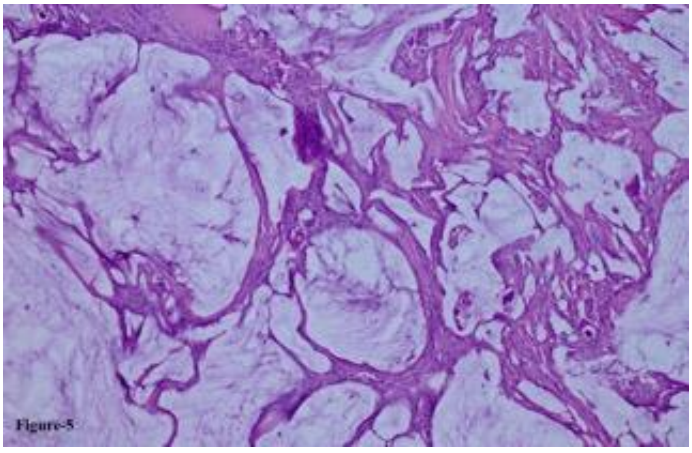

Figure 5: Mucicarmine (+) staining of the tumor. (Mucicarmine stain: x100)

Discussion

Thymic carcinoma is a rare neoplasm of the thymus, and unlike a thymoma, it exhibits malignant features of obvious cytologic atypia, having a more aggressive propensity for early local invasion and wide spread metastases. It includes the following subtypes: Squamous cell carcinoma, lymphoepithelioma-like carcinoma, neuroendocrine carcinoma, adenosquamous carcinoma, clear cell carcinoma, papillary carcinoma, basaloid carcinoma, sarcomatoid carcinoma, and mucoepidermoid carcinoma [4,5]. The most common histologic type is squamous cell carcinoma, usually occurring in middle-aged men [6,7]. Our case was old-aged.

The prognosis of thymic carcinoma is poor because of early metastatic involvement of the pleura, lungs, lymph nodes of the mediastinum, bone and liver [8,9]. In our case, there was only pericardial invasion and the tumor was in pathological stage III according to the staging system of Masaoka. Thus, the present tumor was judged to be potentially completely resectable. Local recurrences and distant metastases are frequent, occurring at 35% and 50%, respectively. The overall survival rate at 5 years for thymic carcinoma is reported to be approximately 35% [6,7]. Thymic carcinomas have been roughly classified as either low or high-grade malignancy [6]. The low-grade tumors with relatively favorable prognoses include squamous cell carcinoma, mucoepidermoid carcinoma and basaloid carcinoma, whereas the high-grade tumors include the others with poor prognosis. Although it appears that mucoepidermoid carcinoma of the thymus is extremely rare, it's histological characteristics have been well analyzed: It is composed of variably sized cysts, lobules, sheets and nests of such tumor cells as epidermoid cells, mucus-secreting cells, and occasionally intermediate type cells in a variable admixture [10,11]. In our case, similar histological and gross features were observed, and this tumor was finally diagnosed as mucoepidermoid carcinoma of the thymus. As described above, thymic mucoepidermoid carcinoma is generally considered to be a low-grade malignancy with a good prognosis [6].

The well-differentiated type, in which mitosis was virtually absent, was not fatal, while the poorly differentiated type was clinically aggressive enough to threaten life, and cellular atypia, mitosis, necrosis, and predominance of an epidermoid component were often observed. The present primary tumor regarded as the poorly-differentiated type because of the mitosis and cellular atypia. Accurate histologic subtyping, namely tumor differentiation as well as clinical staging are highly recommended for the diagnosis and treatment of this disease. Especially, when the tumor is anatomically located in contact with the pleura cavity, more accurate and careful staging may be clinically necessary in the long-term follow-up. If complete resection is possible, this type of tumor should be removed by surgery, as with other types of thymic carcinoma. Complete resection was performed in our case. Takahashi et al [12] reported that in a limited early stage of thymic carcinoma, surgical resection was adequate for treatment, although the rate of complete resection is only 20–35% [7,13,14]. However, if the tumor is advanced or recurrent, a multimodality approach, including surgical resection, radiation, chemotherapy, or a combination selected [14,15]. In our case, after surgery, multimodal therapy including chemotherapy and radiotherapy were performed.

In conclusion, we here in described a rare case of thymic mucoepidermoid carcinoma undergoing multimodality treatment, including surgical resection, irradiation and chemotherapy. Although clinical aspects of this disease are little known, it was assumed that such aggressive therapy contributed to long-term survival.

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Congenital transmesenteric internal hernia; A rare cause of bowel ischemia in adults: A case report

Konjenital transmesenterik internal herni; Erişkinlerde nadir bir barsak iskemi nedeni: Olgu sunumu

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Abstract

Congenital transmesenteric hernias represent a very small group of internal hernias which are uncommon and are a rare cause of bowel obstruction and bowel ischemia in adults with few reported cases in published literature. Preoperative diagnosis of the condition is difficult, early intervention and surgical correction goes a long way in preventing high morbidity and mortality associated with cases of internal hernia. We present a case of true congenital transmesenteric hernia in a 31-year-old woman with no previous surgical history or trauma who presented with history of severe abdominal pain and the cessation of both feces and flatus. The abdominal CT scan could not confirm the diagnosis. The patient was operated upon on account of increasing abdominal pain and distention associated with shock. An exploratory laparotomy revealed a congenital transmesenteric defect through which loops of bowel had herniated and become gangrenous, resulting in resection and a stomy type Bouilly Volkmann.

Keywords: Congenital transmesenteric defect, Internal hernia, Bowel ischemia

Öz

Konjenital transmesenterik fıtıklar, nadir görülen ve yayınlanmış literatürde az sayıda bildirilmiş vaka ile erişkinlerde nadir görülen bir barsak tıkanıklığı ve barsak iskemi nedeni olan çok küçük bir iç fıtık grubunu temsil eder. Hastalığın preoperatif tanısı zordur, erken müdahale ve cerrahi düzeltme, içsel fıtık vakalarına bağlı yüksek morbidite ve mortaliteyi önlemede uzun bir yol kat eder. Daha önce cerrahi öyküsü veya travması olmayan 31 yaşında bir kadın hastada gerçek konjenital transmesenterik herni olgusunu sunuyoruz. Şiddetli karın ağrısı öyküsü ve hem dışkı hem de flatusun kesilmesi ile başvurdu. Abdominal BT taraması tanıyı doğrulayamadı. Hasta abdominal ağrının artması ve şokla ilişkili distansiyon nedeniyle ameliyat edildi. Bir keşif laparotomisi, barsak ilmeklerinin fıtıklandığı ve kangrenli hale gelen doğuştan bir transmesenterik defekti ortaya çıkardı, rezeksiyona ve bir stomi türü Bouilly Volkmann'a neden oldu.

Anahtar kelimeler: Konjenital transmesenterik defekt, İnternal fıtık, Bağırsak iskemi

Introduction

Internal hernia is a rare cause of intestinal obstruction in adults. Of internal hernia congenital transmesenteric hernia only constitute an estimated 5–10% of cases [1]. Congenital transmesenteric internal hernia is a very rare but definite acute surgical condition requiring early diagnosis. In almost all cases presentation is acute intestinal obstruction or recurrent pain abdomen due to mesenteric ischemia without definite clinical symptoms or signs. In published literature only 36 patients have suffered from bowel obstruction and 9 from ensuing ischemia secondary to transmesenteric hernia [2,3]. Almost all reported cases are diagnosed intraoperatively.

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Case presentation

A 31-year-old woman was admitted to general surgery emergency with a five-day history of constipation, progressive abdominal pain, nausea and vomiting. The last bowel movement had been two days ago. There was no significant past medical history especially of chronic constipation, psychiatric disease, trauma or abdominal surgery. There was no other relevant past personal or family history.

On examination, the vital signs were: Temperature 39˚C, Pulse 115/min, Respiratory rate 26/min, Blood pressure 90/60 mmHg. Abdominal examination revealed a distension of the abdomen without signs of peritonitis. The abdomen was tympanic to percussion. There were no umbilical or groin hernias. Digital rectal examination demonstrated an empty rectal vault without intraluminal masses. Further systemic examination was unremarkable. The abdominal X-ray revealed few gas distended bowel loops (Figure 1).

Blood investigations showed leukocytosis at 26.000 e/dl, CRP at 148 mg/l, serum sodium and potassium levels were within normal limits. Functional renal failure: serum urea 0.6 g/l, blood creatinine at 12mg/l.

The abdominal computed tomography: showed crowded and stretched mesenteric vessels, dilated and clustered small bowel, thickened intestinal wall (Figure 2).

4 hours after admission, the patient worsened her abdominal pain and her hemodynamic became unstable. After initial resuscitation with intravenous fluids, analgesics and antibiotics, decision was taken to proceed for an emergency laparotomy.

Intra operative findings approximately 1 m 50 cm of gangrenous small bowel, proximal ileum herniating (Figure 3) through a congenital small bowel mesenteric defect (Figure 4). The hernia was reduced, the mesenteric defect was repaired, small bowel resected and stomy type Bouilly Volkmann performed.

The postoperative course was uneventful. Discharge from hospital was five days following admission. Histopathology revealed hemorrhagic infarction of 145 cm of small bowel and mesenteric vessels showed no evidence of vasculitis or thrombosis. The restoration of intestinal continuity was done two months later with good evolution.

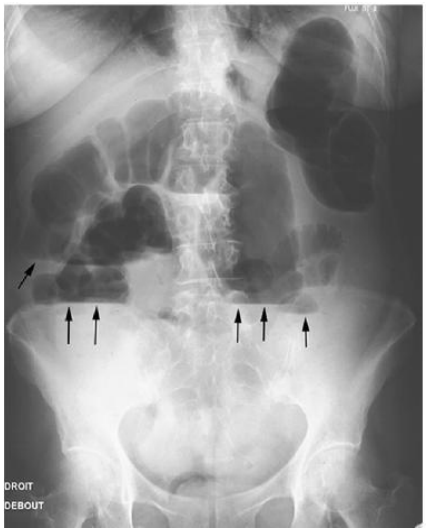

Figure 1: Dilated digestive loops, many seats hydroaeric levels

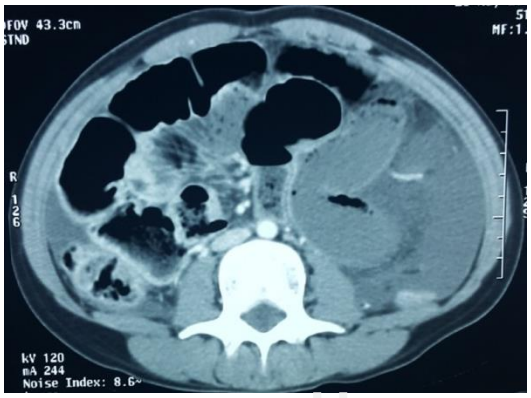

Figure 2: CT scan showed crowded and stretched mesenteric vessels, dilated and clustered small bowel, thickened intestinal wall

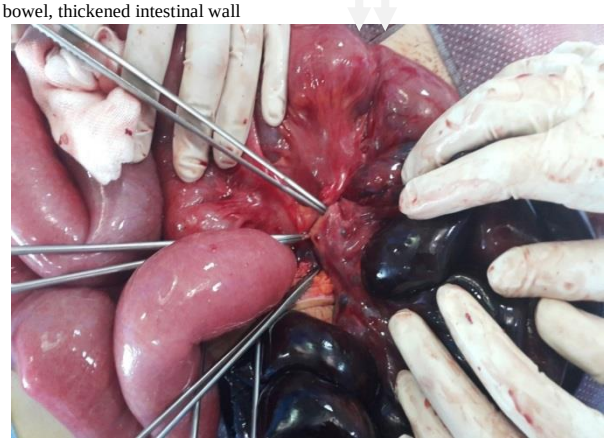

Figure 3: Intraoperative view demonstrating gangrenous small bowel, proximal ileum herniating through a congenital small bowel mesenteric defect

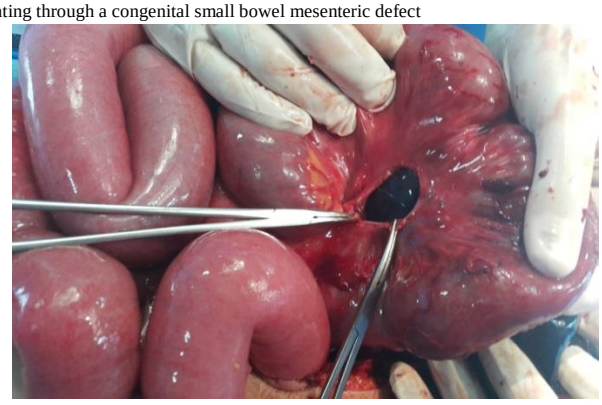

Figure 4: Intraoperative view demonstrating a congenital small bowel mesenteric defect

Discussion

An internal hernia is a protrusion of viscera through a defect or aperture, either mesenteric or peritoneal, and may be either congenital or acquired. Most internal hernia are paraduodenal (53%) and are acquired postoperatively, resulting from incomplete closure of surgically created mesenteric defects [4].

Transmesenteric hernia is a protrusion of viscera through a defect in mesentery of small bowel, transverse colon or sigmoid colon. Congenital internal hernia although rare, they can present at any age, though they are more common in the pediatric population [2]. Is an important cause of small bowel obstruction and its diagnosis is a challenge to both surgeons and radiologists. Congenital internal hernia is usually published as case reports rather than case series.

In 1836 Rokitansky reported first instance of trans-mesenteric internal hernia in an autopsy. Incidence of mesenteric defects is about 0.5% in all autopsies.

The pathogenesis of mesenteric defects is uncertain with one popular hypothesis suggesting the cause may be prenatal

intestinal ischemia and subsequent thinning of the mesenteric leaves, because prenatal intestinal ischemia is associated with bowel atresia in 5.5% of the pediatric population [5]. Alternatively a genetic etiology has been suggested given the association between transmesenteric hernia and other anomalies including cystic fibrosis and Hirschprung's disease [4].

Three main types of transmesenteric internal hernias are seen. The first and most common is the transmesocolic, which has been documented to occur in 0.7–3.25% of patients after laparoscopic Roux-en-Y gastric bypass surgery [6]. The second type of transmesenteric internal hernia occurs when bowel prolapses through a defect in the small-bowel mesentery, it is the same case in our patient. Finally, the third type, known as the Peterson type, has also been described and involves the herniation of small bowel behind the Roux loop before the small bowel eventually passes through the defect in the transverse mesocolon [7].

Transmesenteric hernias are more likely than other subtypes to develop volvulus and strangulation or ischemia, the incidence of which is reported to be as high as 30% and 40%, respectively, with mortality rates of 50% for the treated groups and 100% for the nontreated subgroups [8,9]. Volvulus and strangulation or ischemia may be partly caused by the usual small aperture of the defect (2–5 cm) in addition to the lack of encapsulation of the herniated loops, allowing a large length of small bowel to herniate through the mesenteric defect [8,9]. That's what happened in our case.

Transmesenteric hernias presentation can vary from asymptomatic to simple intermittent episodes of abdominal pain, nausea, diarrheas to acute abdomen with vomiting and even unexpected death [10,11].

X-rays and CT imaging may help in identifying signs of obstruction, volvulus and/or strangulation in patients with internal hernias [11]. Certain CT features represented by clustering of dilated small bowel peripherally without overlying omentum and leading to colonic displacement centrally may be suggestive of transmesenteric hernias [11]. However, final diagnosis will only be confidently achieved intraoperatively [12,13]. In our case, CT findings were suggestive of bowel obstruction with midgut volvulus to be the likely cause.

In literature, majority of transmesenteric hernias present as emergency cases, and surgical intervention with or without bowel resection and mesenteric defect closure is often required [10,12,14]. An early intervention is recommended to prevent unnecessary bowel resections and even death [10-12]. Our patient unfortunately was operated on in the gangrene phase probably due to a delay of management.

Conclusion

Preoperative diagnosis of transmesenteric hernia is difficult due to a lack of specific radiological or laboratory findings to confirm a surgeon's clinical suspicion.

We report a rare case of a 31-year-old woman with a spontaneous transmesenteric hernia of proximal ileum with associated gangrene of bowel caused by a congenital mesenteric defect. The insidious onset of this surgical emergency reaffirms the importance of surgeons maintaining a high index of suspicion for a transmesenteric hernia in patients with non-specific clinical and radiological signs.

Misdiagnosis and subsequent delayed exploration may lead to bowel ischemia and subsequent mortality, prognosis being directly correlated with the delay in diagnosis and treatment.

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Case report
Olgu sunumu

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Unilateral surgical approach for lumbar disc herniation with contralateral symptoms: Two case reports

Karşı taraf semptomları olan lomber disk hernileri için tek taraflı yaklaşım: İki olgu sunumu

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Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastadan yazılı onam alındığını ifade etmiştir.

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Abstract
Lumbar disc herniation is the most common cause of the lumbar radicular pain and it is usually encountered on the same side with its symptoms. However, lumbar disc herniation with contralateral symptoms is sometimes observed too. This situation may cause a dilemma for spine surgeons. There are no consensus about cause of the pathophysiology of contralateral radiculopathy, and which surgical approach may suitable for these patients. In here, we present two case reports lumbar disc herniation with contralateral symptoms and discuss this phenomenon in the light of the literature.
Keywords: Lumbar disc herniation, Contralateral symptoms, Unilateral surgical approach

Öz
Lomber disk hernileri, lomber radiküler ağrının en yaygın nedenlerindendir ve sıklıkla lomber disk hernisi ile semptomları aynı tarafta karşılaşılır. Fakat bazen lomber disk hernisi karşı taraf semptomları ile de gözlemlenebilir. Bu durum, omurga cerrahları için bir ikileme neden olabilir. Çünkü, karşı taraf radikülopatinin patofizyolojisinin nedenleri ve hangi cerrahi yaklaşımın bu hastalar için uygun olduğu ile ilgili bir konsensus yoktur. Burada karşı taraf semptomu olan 2 lomber disk olgusu sunulacak ve bu fenomen literatür eşliğinde tartışılacaktır.
Anahtar kelimeler: Lomber disk hernisi, Karşı taraf semptom, Tek taraflı yaklaşım

Introduction

Lumbar disc herniation (LDH) is the most common cause of the radicular pain and it is usually encountered on the same side with its symptoms [1]. However, LDH, which causes contralateral radiculopathy, is sometimes observed [2]. Surgeons usually choose to explore both sides to be certain they do not miss a lesion [3-6]. On the other hand, some surgeons report that exploration of LDH and micro-discectomy are enough to recover from contralateral symptoms [1,7]. Therefore, this situation presents a dilemma for surgeons when they make a decision about which side to choose to approach. Several authors have reported some patients with LDH having contralateral symptoms and have suggested many hypotheses about LDH causing the contralateral radiculopathy [1,2,4,7-10]. In this study, we present two case reports and explain the LDH with contralateral radiculopathy.

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Case presentation

Case 1

A 57-year-old male patient admitted to hospital because of weakness in his left foot. His complaints had started one month ago. Left food weakness (4/5), and pain on the L4 dermatome were identified in his neurological examination. Patient's Preoperative Visual Analog Score (VAS) was 9. Lumbar Magnetic Resonance Imaging (MRI) was performed, and right paracentral disc herniation was identified on the L3-4 level (Figure 1A). And then, we decided to perform Electromyography (EMG) to identify which roots were affected. EMG showed us isolated left L3 chronic and L5 acute motor unit potential changing. We suggested an operation, and informed patient consent was received from the patient. In the operation, right L3 laminotomy, flavetomy and microdiscectomy were performed with operation microscope. Post-operative VAS was 1. The patient was discharged two days after the surgery. The weakness in the left ankle recovered one month after the surgery, and lumbar MRI control was performed (Figure 1B).

Case 2

A 34-year-old male patient admitted to hospital with pain in the left leg, and weakness in the left foot. The patient's complains had started two months ago with pain in the left leg, and then weakness in the left foot. Neurological examination was performed, and the straight leg raising test was positive in 10 degree (Preoperative VAS: 8), and left foot plantar flexion (4/5) weakness were identified. Lumbar MRI was performed preoperatively, and L5-S1 mediolateral extrude disc fragmentation was identified (Figure 2A). And then, we suggested to perform EMG to identify which roots were affected. EMG showed us isolated left S1 acute motor unit potential changing. Operation was suggested, and informed patient consent was received from the patient. In the operation, right L5-S1 microdiscectomy was performed, and the patient's complaints (post-operative VAS: 1) and weakness recovered after the surgery. Lumbar MRI control was performed just after the surgery (Figure 2B).

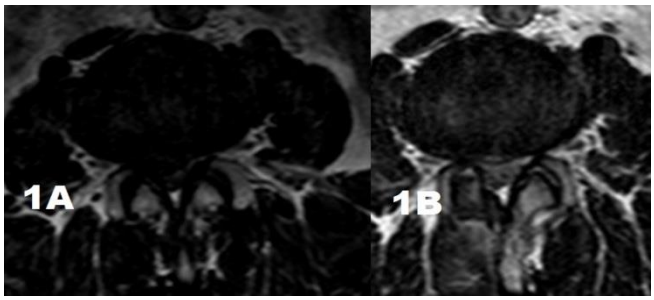

Figure 1: Axial T2-weighted magnetic resonance image through the L3-L4 disc showing the right mediolateral disc herniation (1A). postoperative lomber MRI one month later after surgery (1B)

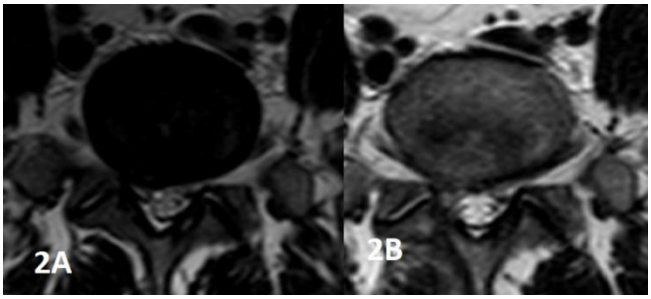

Figure 2: Axial T2-weighted magnetic resonance image through the L5-S1 disc showing the right mediolateral disc herniation (2A). Postoperative lomber MRI one month later after surgery (2B)

Discussion

Various hypotheses have been suggested to explain the pathophysiology of LDH with contralateral symptoms [1,2,4,7-10]. Kornberg has suggested that in the absence of dural attachments to the posterior longitudinal ligament, which also fixes the nerve root, the contralateral nerve roots are affected in the space of the lateral recess [4]. Sucu et al. [7] and Kim et al. [11] have suggested that traction may be responsible for the emergence of the contralateral symptoms rather than direct compression. Because, an apex of disc herniation laterally deviated away from the symptomatic side. Contrary to Kornberg, Akdeniz et al. [1] has suggested that more dural attachments on the posterior longitudinal ligament than usual could cause the fixing and trapping of the contralateral side of the nerve root and in the absence of the dural attachments, the nerve root may partially escape from the disc, but if it is anchored with attachments, it cannot. Therefore, the nerve root may be entrapped in the lateral recess by traction forces (similar with the double crush syndrome). Kalemci et al. [2] have suggested that venous congestion may be a factor for contralateral symptom. It was suggested in a clinical and morphometric study conducted by Karabekir et al. [9] that an asymmetrically hypertrophied ligamentum flava might be the causing factor. The migrated epidural fat hypothesis has been suggested by Yang et al. [8] and the lateral recesses stenosis and friction radiculitis have been suggested by Hasegawa et al. [10].

However, in many suggested hypotheses about LDH with contralateral symptoms, there is no consensus about surgical approach side or sides and the pathophysiology. Some authors like Choudhury et al. [3], Kornberg [4], Mirovsky and Halperi [5] performed bilateral explorations to do not miss a lesion. However, Sucu and Gelal [7], Akdeniz et al. [1], and Karabekir et al. [9] performed the operative approach only on the lumbar disc herniated side and reported that exploration of the LDH side with microdiscectomy was enough for the recovery of the contralateral symptoms.

In our opinion, the hypothesis that will explain the contralateral symptom findings must support the following 3 questions: First question: Can there be a relation between the direction of the apex of the disc and the contralateral symptom? Second question: Why were there no symptoms in the side where the disc was clear? Third question: Can there be a similarity between the formation pathophysiology of the contralateral symptom in the lower segments except the next level of the level where the disc come out-, and the contralateral root pathophysiology neighboring the segment where the disc came out? In our opinion, as Sucu and Gelal [7] explained previously in their case series, there is a relation between the apex of the disc and the contralateral symptom; however, in addition to this, we also think that the apex of the disc may cause asymptomatic root findings -except the expectations- showing root pressure radiologically. Because, depending on the direction of the apex at the moment of its beginning, its pushing the root to the posterio-lateral in the asymptomatic side may also cause the movement of symptomatic root in the contralateral side towards dorsomedial. The movement of the asymptomatic root towards dorsolateral causes the asymptomatic root approach towards the pedicule and makes the root become stuck in the lateral recess

and decreases its stretching. Contrary to this, the movement of the root in the contralateral side towards the dorsomedial causes the root move away from the pedicule, and therefore may cause stretching in the contralateral root, and may also cause secondary injury by pressing the root in the lateral recess. In addition to this, the secondary caudal fiber findings may be in the front line in the pressure on the contralateral caudal fibers rather than the traction forces in the appearance of the contralateral symptoms in the lower segments of the level where the disc has come out. Because, while the caudal fibers of the lower level act freely within the dura in normal conditions, they may cause hypertrophy in disc hernias with wide-base medium-line discs, or cause contralateral lower level root findings as secondary to compression by being squeezed between the degenerated ligamenta flava.

As in our first case presentation, it is observed that there is a ligamenta flava hypertrophied at the same level together with the size of the medium-line component of the disc. These radiological findings support the hypothesis that the traction force may be in the front line in the appearance of the contralateral root findings at next level related with the direction of the apex of the disc; however, in the appearance of lower level contralateral root findings -except the next level-, the compression forces may be effective. Our second case presentation supports the hypothesis that the traction force is in the front line in the appearance of contralateral root findings in situations where the medium-line pressure is not clear. Since we think that -similar to the literature- the disc is an etiological factor in the appearance of contralateral root findings, we approached to the disc from the herniation side in the easiest way with microdiscectomy to not to cause additional complications. The examination and radiological findings of the patients in the postoperative period support the authors claiming that the excision of the disc with microdiscectomy from the side where it is clear is sufficient in these types of patients.

Conclusion

As a result, we can conclude that in the formation of contralateral symptoms, not only the traction but also the compression force may be influential. Especially, the traction force may be in the front line in the initial appearance of contralateral findings depending on the medium-line size and the direction of the apex of the disc. In patients with contralateral lower segment findings, on the other hand, contralateral root findings secondary to the contralateral caudal fibers pressure might appear depending on the size of the medium-line component of the disc and on the effect of the ligamenta flava which is hypertrophied or degenerated. In cases that do not have the same or lower level foraminal stenosis and lateral recess syndrome, excising the disc with microdiscectomy by approaching it from the side where it is clear may help them to relive their complaints.

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