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Use of vaginal creatinine levels in detecting premature rupture of membranes

Erken memran rüptürü tespitinde vajinal kreatinin seviyelerinin kullanılması

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Abstract

Aim: Misdiagnosis is frequent in premature rupture of membranes (PROM) patients. The most accurate diagnosis of PROM requires reliable laboratory tests. Due to the lack of a gold-standard diagnostic method, many methods have been proposed in this regard. The aim of this study is to determine an easy diagnostic method in early membrane rupture and to determine the usability, reliability and cut-off values of vaginal creatinine measurements in the detection of PROM compared to vaginal placental alpha microglobulin-1 (PAMG-1) test.

Methods: We designed a cross-sectional study. A total of 63 patients admitted to the Obstetrics and Gynecology Clinic of Samsun Ondokuz Mayıs University with suspected PROM between 15 November 2012 and 15 June 2013 were included in this study. Following anamnesis, all patients were vaginally subjected to PAMG-1 (AmniSure® ROM) test with sterile speculum and injected with 5 cc of saline into the vagina, and then, a 3 cc sample was retrieved with the same injector and put into a biochemistry tube. Immediately thereafter, the material was sent to the biochemistry laboratory, centrifuged and stored at -70 ^{0}C until all samples were studied. The patients were classified as PROM and non-PROM based on the positive or negative result of PAMG-1 test. Following this classification, the patients were also grouped as PROM and non-PROM according to their vaginal creatinine values.

Results: The mean maternal age of our patients was 26.3 years in the PROM group and 28.8 years in the non-PROM group. The mean gestational weeks were 30.8 weeks in the PROM patients and 32.5 weeks in the non-PROM patients. Of 20 patients subjected to PAMG-1 test for PROM diagnosis, 17 were PAMG-1 and creatinine positive while 3 were PAMG-1 negative and creatinine positive. Of 43 patients subjected to PAMG-1 test, 42 were PAMG-1 negative while 1 was PAMG-1 positive and creatinine negative. Accordingly, vaginal creatinine was found to have 94.4% sensitivity, 93.3% specificity, 85% positive predictive value, and 97.7% negative predictive value in PROM diagnosis. The mean creatinine values in the PROM and non-PROM groups were 0.39 (0.31) mg/dl and 0.04 (0.10) mg/dl, respectively (P=0.05).

Conclusion: Creatinine assessment in vaginal flushing fluid can be a cheaper, faster, easily accessible and highly accurate test with 94.4% sensitivity and 93.3% specificity in PROM diagnosis.

Keywords: Creatinine, Premature rupture of membranes, Placental alpha microglobulin-1

Öz

Amaç: Erken membran rüptürü (EMR) bulunan hastaların teşhisinde yanılgılar sık görülebilmektedir. EMR tanısını en doğru şekilde koymak için güvenilir laboratuvar testleri gerekir. Altın standart bir tanı metodunun olmaması yüzünden bu konuda birçok yöntemler öne sürülmüştür Bu çalışmada EMR teşhisinde vajinal kreatinin ölçümlerinin %100 yakın güvenirlikle kullanılan vajinal Plasental Alfa mikroglobulin-1 (PAMG-1) testine göre kullanılabilirliği, güvenirliği ve cut off değerlerinin tespiti hedeflenmiştir

Yöntemler: Bu çalışmaya, Samsun Ondokuz Mayıs Üniversitesi Kadın Hastalıkları ve Doğum Kliniği'ne 15 Kasım 2012 – 15 Haziran 2013 tarihleri arasında başvuran toplam 63 EMR şüpheli hasta dahil edilmiştir. Tüm hastalara anamnezi takiben steril spekulum ile vajinal olarak PAMG-1 (AmniSure ® ROM) testi ve ardından vajene 5 cc serum fizyolojik enjekte edilip sonrasında 3 cc aynı enjektörle geri alınarak biyokimya tüpüne koyulmuştur. Hemen ardından materyal biyokimya laboratuvarına gönderilip santrifüj edildikten sonra dondurucuda -70 ^{0}C derecede tüm numuneler çalışılıncaya kadar saklanmıştır. Hastalar Plasental Alpha Mikroglobulin-1 (PAMG-1) testinin pozitif ve negatif olup olmamasına göre EMR olan ve EMR olamayan olarak sınıflandırıldı. Bu sınıflamanın ardından vajinal kreatinin değerine göre de hastalar EMR ve EMR olmayan olarak gruplandırıldı.

Bulgular: Olgularımızın ortalama maternal yaş değeri EMR olan hasta gurubunda 26,3 yaş, EMR olmayan gurupta 28,8 yaş idi. EMR olan hastalarda gebelik haftası ortalama değeri 30,8 hafta, EMR olmayan hastalarda ise 32,5 hafta idi. EMR tanısı amaçlı PAMG -1 testi uygulanan 20 hastanın 17 sinde PAMG-1 ve kreatinin pozitif, PAMG-1 negatif olan 3 hastada kreatinin pozitifti. PAMG-1 testi uygulanan 43 hastanın 42 sinde PAMG-1 negatif, 1 inde PAMG-1 pozitif ve kreatinin negatifti. Bu sonuçlara göre vajinal kreatinin EMR teşhisinde %94,4 sensitivite, %93,3 spesifisite, %85 pozitif prediktif değer, %97,7 negatif prediktif değer olarak hesaplandı. EMR olan ve olmayan gurupta ortalama kreatinin değerleri sırasıyla 0,39 (0,31)mg/dl ve 0,04 (0,10) mg/dl (P=0,05).

Sonuç: Vajinal yıkama sıvısında kreatinin ölçümü EMR tanısında daha ucuz, hızlı, kolay ulaşılabilir ve %94,4 sensitivite, %93,3 spesifisite ile yüksek doğruluk oranına sahip bir test olabilir.

Anahtar kelimeler: Kreatinin, Erken membran rüptürü, Plasental alfa mikroglobulin-1

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Introduction

Premature rupture of membranes (PROM) is defined as the rupture of fetal membranes before the onset of uterine contractions required for labor [1,2]. If PROM occurs before the 37th gestational week, it is called preterm PROM (PPROM). The PROM incidence is 5-10% of all births [3,4]. 60-80% of PROM occurs in term pregnancies and 20-40% in pregnant women before the 37th week. Although PPROM is observed in 3% of all pregnancies, it is responsible for or relevant to one third of preterm births. This rate further increases in multiple pregnancies [5]. PPROM is the most frequent cause of preterm births [6]. Despite the advances in medicine and technology, PROM and especially PPROM are still two troublesome issues causing therapeutic dilemmas in modern obstetrics, and they bring about several problems. These problems include prematurity, perinatal infections, oligohydramnios, umbilical cord compression, pulmonary immaturity, and the resulting risks associated with fetus such as increased perinatal mortality and morbidity. In addition, there are maternal risks such as increased cesarean section rate, choriodecidual infection, and placental decollement [7,8]. Misdiagnosis is frequent in PROM patients. While false positive results may lead to unnecessary interventions such as hospitalization or even the induction of labor, false negative results prevent or delay taking necessary obstetric measures such as the treatment of maternal infection [9,10].

The most accurate diagnosis of PROM requires a good history, physical examination and reliable laboratory tests. Due to the lack of a gold-standard diagnostic method, many methods have been proposed in this regard [4,11-15]. Previously, the combination of amniotic fluid pooling in the speculum examination, nitrazine test for pH determination, and fern tests based on microscopic evidence were used in the diagnosis of PROM. However, false positive results in these tests due to contamination with blood, semen and urine are substantial. Furthermore, there is gradually less diagnostic accuracy in the period following the rupture of membranes [16,17]. Such problems in diagnosis have paved the way for numerous tests that use biochemical markers. In search for a gold standard, alpha-fetoprotein (AFP), B-hCG, vaginal prolactin, fetal fibronectin, insulin-like growth factor binding protein-1, and placental alpha microglobulin-1 (PAMG-1) immunoassay tests have been the subject of many studies. In addition, although ultrasonography-guided intra-amniotic injection of indigo carmine is an effective test, its association with risk factors such as placental decollement, infection, iatrogenic PROM, and fetal loss has restricted its use. In recent years, PAMG-1 has come to the forefront among other non-invasive diagnostic methods in PROM diagnosis for reasons such as its high concentration in amniotic fluid and low concentration in the blood, and its low concentration in the cervicovaginal fluid while fetal membranes are intact. Although it is one of the most valuable diagnostic methods at the moment, its low popularity and expensiveness are regarded as its disadvantages.

Creatinine assessment in vaginal fluid has been the subject of several studies. Most of the amniotic fluid is formed by the transfer of fetal urine into the amniotic fluid as of the second half of the pregnancy. Urea, creatinine, and uric acid blend into amniotic fluid at high concentration through fetal urine. The mean creatinine value in amniotic fluid in early gestational period was found to be 0.6 mg/dl. This is equal to the creatinine value in the maternal blood [18]. The creatinine concentration in amniotic fluid increases very rapidly between 20th and 32nd weeks and reaches 2-4 times the value in the maternal blood [12]. When the threshold value of creatinine concentration in vaginal flushing fluid was accepted as 0.12 mg/dl in the study conducted by Gürbüz et al. [12], and the value of creatinine concentration was accepted as 0.6 mg/dl in the study conducted by Kafalı et al. [19], sensitivity, specificity, and positive and negative predictive values were found to be 100% in both studies. A study conducted by Zanjani et al. [20] found 96.7% sensitivity, 100% specificity, 100% positive predictive value and 96.8% negative predictive value when the threshold value of creatinine concentration was taken as 0.5 mg/dl. Moreover, creatinine value ranging between 1.5 and 2.0 mg/dl in the amniotic fluid was also observed as a symptom of fetal maturity [21]. In these studies, creatinine accuracy was identified in comparison to clinical assessment, nitrazine test and fern test. However, creatinine does not present the true diagnostic value due to the high false positive and negative rate of these conventional tests, and it has not been compared to tests such as PAMG-1 test with about 100% accuracy in the studies conducted on the use of vaginal creatinine levels in the PROM diagnosis..

Therefore, with this study, we aimed to compare PAMG-1 test, which is one of the recent diagnostic methods that can be considered as the gold standard but is expensive, less accessible, and with about 100% diagnostic accuracy, with creatinine in vaginal flushing fluid, which is more accessible, cheaper and with accuracy proven in recent studies.

Materials and methods

This article was approved by the Ethics Committee of the Faculty of Medicine of Ondokuz Mayıs University. Study type is "cross-sectional study". This study was carried out on 81 pregnant women admitted to Obstetrics and Gynecology Clinic at Samsun Ondokuz Mayıs University between 15 November 2012 and 15 June 2013. All the patients were given detailed information about the purpose of our study, the procedures to be followed and the estimated results of these procedures, and asked to sign the consent forms.

Women in the 20th-40th weeks of pregnancy who had water breaking complaint or referred with suspected water breaking were included in the study. 9 patients with vaginal bleeding, 3 patients with placenta previa and 6 patients lost to follow-up were excluded from the study. The study was carried out with a total of 63 patients.

Inclusion criteria

No history of preterm labor and premature rupture of membrane in previous pregnancies, pregnancy being in its second or third trimester, no fetal or placental pathology, no previously detected uterine pathology or malformation

Exclusion criteria

A significant amount of vaginal bleeding, presence of placenta previa, multiple pregnancies, no regular follow-up visits

All patients underwent vaginal examination with sterile speculum following the anamnesis. In vaginal examination, the

patients were evaluated for fluid pooling, fluid drainage from cervix during the Valsalva maneuver, cervical dilatation and effacement, cervicitis, vaginitis, blood, urine, meconium, and presence of semen. Next, the patients, who were admitted to our clinic with the complaint or pre-diagnosis of suspected water breaking, were subjected to the PAMG-1 test, which is implemented routinely in our clinic and has high diagnostic accuracy. Immediately afterwards, a vaginal flushing sample was taken for creatinine. Later, amniotic fluid indices (AFI) were assessed and recorded via ultrasonography with the four-quadrant technique. Demographics and obstetric characteristics of the patients such as maternal age, gravidity and parity were asked about and recorded in their first examinations.

Implementation of the PAMG-1 test

AmniSure ® ROM (Rupture of (fetal) Membranes Test) (International LLC, USA) test kit was used for PAMG-1 sampling. The kit includes one sterile polyester cotton swab, one tube containing sample resolution solution (0.5 ml), and one strip test in package. After the speculum was attached and the vagina and cervix were observed for sampling, the polyester tip of the cotton swab was inserted into the posterior vagina, holding the middle of the sterile polyester cotton swab and ensuring that it did not touch anywhere. A swab sample was also taken from the external cervical os surface and vaginal margins, and the cotton swab was removed from the vagina one minute later. With its polyester tip placed in the bottle containing the resolution solution, the cotton swab was rinsed by rotating for one minute. The cotton swab was then removed from the solution and disposed of, and the arrowed white tip of the test strip was plunged into the solvent vial for not less than five minutes and not more than ten minutes. If the test strip was clearly visible in the vial, it was removed after not less than five minutes, or once ten minutes were fully up. The test strip was placed on a clean, dry, flat surface, and the result was read and recorded. If only one control line was visible, the test result was considered negative; if both the control and test lines were visible, the test result was considered positive; and if no line was visible, the test result was considered invalid and the test was repeated.

Sampling for creatinine in vaginal fluid

Without removing the speculum after the PAMG-1 test, 5 cc saline was injected into the vagina, and then, 3 cc was retrieved into the biochemistry tube with the same injector. Immediately thereafter, the material was sent to the biochemistry laboratory, centrifuged and stored at -70 ^{0}C until all samples were studied.

The patients were classified as PROM and non-PROM based on the positive or negative result of PAMG-1 test. Following this classification, the patients were also grouped as PROM and non-PROM according to their vaginal creatinine values.

Statistical analysis

The data obtained from the study were coded, recorded and analyzed using SPSS (Statistical Package for Social Sciences) 15.0 software package. For data evaluation, continuous variables were expressed in mean (standard deviation) while the frequency data were expressed in numbers (%). Kruskal-Wallis, Mann Whitney U, N-Par and Chi-Square tests were used for statistical analysis. $P<0.05$ was accepted as the level for statistical significance.

Results

The gestational weeks of 63 patients who participated in our study were between 22 weeks and 36 weeks and 5 days. Following the PAMG-1 test, patients were classified as PROM and non-PROM. 18 patients were found to have PROM whereas PROM was not detected in 45 patients. PROM and non-PROM patients were demographically evaluated in the following tables. Table 1 shows the numerical distribution of the presence of PROM by gestational weeks according to being PAMG-1 positive or negative.

Table 1: Distribution of PROM by gestational weeks according to being PAMG-1 positive or negative

Gestational week	PROM	Non-PROM	Total	*P*-value
20- 27+6 weeks	4 (22.2%)	7 (15.6%)	11 (17.46%)	0.51
28-31+6 weeks	4 (22.2%)	8 (17.8%)	12 (19.04%)	0.52
32-35+6 weeks	8 (44.4%)	18 (40%)	26 (41.33%)	0.55
36-37 weeks	2 (11.1%)	12 (11.1%)	14 (22.22%)	0.58
TOTAL	18 (100%)	45 (100%)	63 (100%)	

No statistically significant difference was found between PROM and non-PROM patients who were admitted to our clinic by gestational weeks according to PAMG-1. 26 (41.33%) of the patients were pregnant for 32-36 weeks. In figure 1, presence of PROM is schematized by gestational weeks.

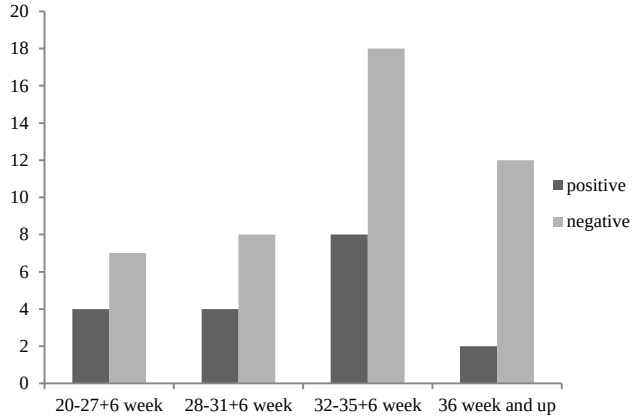

Figure 1: Numerical distribution of PROM by gestational weeks

The mean maternal age of our patients was 26.3 years in the PROM group and 28.8 years in the non-PROM group. The mean gestational weeks were 30.8 weeks in the PROM patients and 32.5 weeks in the non-PROM patients (Table 2).

Table 2: Comparison of mean maternal age and mean gestational weeks in terms of being PAMG-1 positive or negative

	PROM	Non-PROM	*P*-value
Maternal age Mean (SD), year)	26.38 (4.1)	28.08 (5.0)	0.23
Gestatıonal week Mean (SD), week)	30.84 (4.52)	32.54 (4.08)	0.24

No statistically significant difference was observed between the PROM and non-PROM patients by mean maternal age ($P=0.23$). There was no statistically significant difference between the PROM and non-PROM patients by mean gestational weeks ($P=0.24$). Mean cervical effacement of our patients was 34.4% in the PROM group and 16.6% in the non-PROM group. Mean cervical dilatation was 1.5 cm in the PROM group and 0.7 cm in the non-PROM group. Mean amniotic fluid index was 61.6 in the PROM group and 73.1 in the non-PROM group. Table 3 shows the mean values of cervical dilatation, cervical effacement and amniotic fluid index for PROM and non-PROM groups.

Table 3: Comparison of mean values of cervical dilatation, cervical effacement and amniotic fluid index in terms of being PAMG-1 positive or negative

	PROM	Non-PROM	*P*-value
Cervical effacement Mean (SD), %)	34.44 (18.22)	16.67(20.56)	0.01
Cervical dilatation Mean (SD), cm)	1.5 (0.70)	0.76 (0.95)	0.01
Amnion fluid index Mean (SD)	61.67 (26.40)	73.11(42.51)	0.48

Mean cervical dilatation and mean cervical effacement were significantly higher in the PROM group (P=0.01). This difference was attributed to the onset of labor in the PROM patient. This difference was attributed to the onset of labor in the PROM patient. There were no statistically significant differences between mean amniotic fluid indices (P=0.48). The reason was associated with the fact that the patients were referred to our clinic either for the complaint of water breaking or the suspicion of oligohydramnios-related water breaking. 22 of our patients were nulligravida. 7 of the nulligravida were in the PROM group and 15 in the non-PROM group. 41 patients were multigravida. 11 of the multigravida were in the PROM group and 30 in the non-PROM group (Table 4).

Table 4: Comparison of patients' gravidity status in terms of being PAMG-1 positive or negative

	PROM	Non-PROM	Total	*P*-value
Nulligravida	7 (38.88%)	15 (33.33%)	22 (34.92%)	0.92
Multigravida	11 (61.11%)	30 (66.66%)	41 (65.07%)	0.95

No significant difference was found in gravidity by the presence or absence of PROM in the patients (P=0.92 and P=0.95, respectively). As shown in figure 2, 38.8% of the patients suspected of PROM and accepted as having PROM were nulligravida, and 33.33% of the non-PROM patients were observed to be nulligravida.

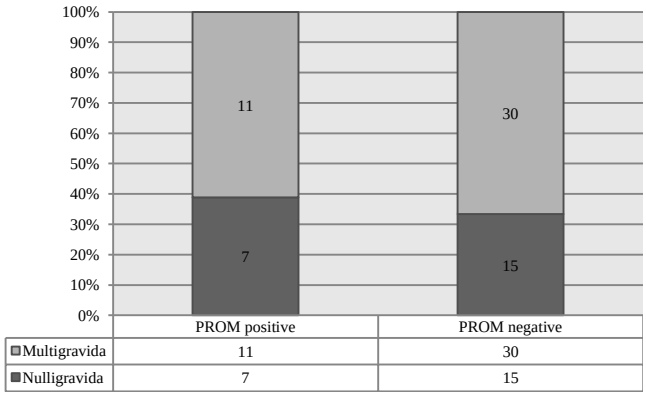

Figure 2: Gravidity distribution of the patients according to being PROM positive or negative

25 of our patients were nullipara. 8 of the nullipara were in the PROM group and 17 in the non-PROM group. 38 patients were multipara. 10 of the multipara were in the PROM group and 28 in the non-PROM group. The patients' parity status is compared according to the presence or absence of PROM in table 5.

Table 5: Comparison of patients' parity status in terms of being PAMG-1 positive or negative

	PROM	Non-PROM	Total	*P*-value
Nullipara	8 (44.44%)	17 (37.77%)	25 (39.68%)	0.55
Multipara	10 (55.55%)	28 (62.2%	38 (60.31%)	0.58

There was no significant difference between the parity statuses of the patients by the presence or absence of PROM. 44.4% of the patients suspected of PROM and accepted as having PROM were nullipara, and 37.7% of the non-PROM patients were observed to be multipara.

The mean time between sampling and delivery was 14.4 days in the PROM patients, and 27.4 days in the non-PROM patients. No statistically significant difference was found between these two groups. However, the median value of the time between sampling and delivery was observed to be 1 day in the PROM patients, and 21 days in the non-PROM patients. In table 6, the time between sampling and delivery was compared according to being PROM positive or negative.

Table 6: Comparison of the time between sampling and delivery according to the presence or absence of PROM

	PROM		Non-PROM	
Time between sampling and delivery (days)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)
	14.4 (31.6)	1 (0.25-112)	27.4 (22.37)	21 (0.25-106)

A statistically significant difference was observed between the vaginal flushing fluid creatinine levels of the PROM and non-PROM patients. In our study, mean creatinine level in vaginal flushing fluid was 0.39(0.31) mg/dl in the PROM group, and 0.04 (0.10) mg/dl in the non-PROM group (Table 7). Figure 3 shows the distribution of mean creatinine level in vaginal flushing fluid according to the presence or absence of PROM.

Table 7: Mean creatinine levels in the PROM and non-PROM groups

	PROM	Non-PROM	*P*-value
Creatinine mg/dl (SD)	0.39 (0.31)	0.04(0.10)	0.06

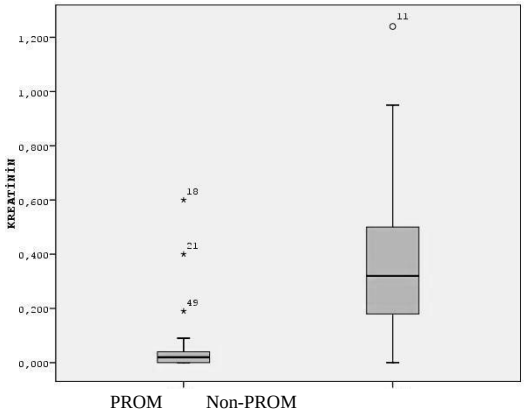

Figure 3: Distribution of mean creatinine levels in vaginal flushing fluid according to the presence or absence of PROM

Creatinine levels in vaginal flushing fluid in the patients classified as being PROM and non-PROM according to the PAMG-1 test were analyzed using ROC curve. According to the analysis results, when the creatinine cut-off value was taken as 0.1050 mg/dl, the patients with 0.1050 mg/dl or higher creatinine cut-off value were accepted as having PROM while the patients with creatinine cut-off value lower than 0.1050 mg/dl were accepted as having no PROM. Accordingly, 17 of 18 PAMG-1-positive patients were found to be vaginal flushing fluid creatinine positive. 42 of 45 PAMG-1-negative patients were found to be vaginal flushing fluid creatinine negative.

All things considered, when the cut-off value of creatinine in vagina flushing fluid was taken as 0.1050 at the end of the ROC curve analysis and compared with the PAMG-1 test, sensitivity, specificity, positive and predictive values were found to be 94.4%, 93.3%, 85%, and 97.7%, respectively (Table 8).

Table 8: Accuracy of creatinine in vaginal flushing fluid compared to PAMG-1 test

		PAMG-1		
		Positive	Negative	Total
Creatinine	Positive	17	3	20
	Negative	1	42	43
	Total	18	45	63

Sensitivity: 94.4%, Specificity: 93.3%, Positive predictive value: 85%, Negative predictive value: 97.7%, Total diagnostic value: 93.6%

Discussion

The incidence of PROM is 5-10% of all births [3,4]. Preterm PROM is observed in 3% of all pregnancies, but it is responsible for or associated with one third of preterm births [17]. Preterm PROM affects 120,000 pregnant women in the United States every year. It is associated with maternal, fetal, neonatal morbidity and mortality as it causes infection, umbilical cord compression, placental decollement, and prematurity. Therefore, a rapid and accurate diagnosis of PROM is very important. The majority of patients can be diagnosed with PROM upon observation of vaginal pooling and amniotic fluid leaking from cervix during speculum examination. However, when vaginal amnion leakage is not observed or when intermittent or minimal amnion leakage is observed, the diagnosis is suspicious. Bleeding, vaginal discharge, semen, and urine make the diagnosis difficult [17].

In 90% of the cases, PROM can be diagnosed through anamnesis, physical examination or conventional methods [17,8]. In cases where PROM cannot be diagnosed by conventional methods, the presence or absence of amniotic fluid in vaginal fluid should be determined quickly and reliably in order to confirm the PROM diagnosis. As an alternative to conventional methods such as nitrazine (pH) test, fern test, and pooling, which are commonly used in the diagnosis of PROM, the presence of proteins such as IGFB*P*-1, AFP, prolactin, fetal fibronectin and hCG, which are components of amniotic fluid, have been investigated in vaginal fluid. Since there is no test that can show rupture of membranes, especially cases of micro-rupture, at 100%, it is often not easy to make the right decision about the sensitivity and specificity of these tests [22]. PAMG-1 assay in vaginal fluid differs in this respect. There is no need for additional instrument or trained personnel to perform the test. As its diagnostic accuracy rate has been determined to be 99% in many studies, it has been approved and used as the most valuable diagnostic method today [4,23]. PAMG-1 was isolated in amniotic fluid by Petrunin et al. [24] in 1975 for the first time obtained the anti-PAMG-1 antibody and assessed the protein content and concentration in amniotic fluid at different stages of pregnancy with immunochemical methods.

Due to its high concentration in amniotic fluid, low concentration in blood, very low concentration in cervicovaginal fluid while fetal membranes are intact, and so on, PAMG-1 has been purposefully used as a diagnostic test in PROM cases. To minimize the false results in the test used in this study, two monoclonal antibodies that adjust the sensitivity level at the optimal low level were chosen. These low values were used to determine the amniotic fluid value of extremely low amounts in vaginal secretions (0.0025-0.00025 ml can determine the amount of amniotic fluid in 1 ml vaginal secretion). Background concentration of PAMG-1 using this combination of monoclonal antibodies is approximately 50- 220 picograms (0.05-0.22 ng) per 1 ml of vaginal fluid. The sensitivity cross section of the test is 5-7 ng/ml, which is at least 20 times higher than the ground-level concentration. It was ensured with this range to remove false negative and false positive results efficiently. In addition to the PAMG-1 test, another effective test is the IGFB*P*-1 (Insulin-like growth factor binding protein-1) test, which is more common in Europe than in the United States. This test has also high accuracy. In various studies, its sensitivity was found in the range of 93-98%, its specificity in the range of 95-100% and its positive predictive value about 98% [14,25,26]. However, in a meta-analysis study conducted in 2013, PAMG-1 test was found to be more accurate than IGFB*P*-1 test [27].

Based on these data, we routinely perform PAMG-1 test to confirm our diagnosis of patients suspected of having PROM in our clinic. We group the patients as having PROM and no PROM according to whether PAMG-1 test is positive or negative, and evaluate them accordingly. As the main theme of our study, we wanted to compare PAMG-1, through which we consider patients as positive or negative, with a cheaper, more accessible and applicable method with the same accuracy. In this regard, we thought that creatinine assessment in vaginal flushing fluid, which is proved by different studies in new publications, can be useful and effective. Previous studies on creatinine have found different cut-off values to diagnose PROM patients. We compared it with highly accurate PAMG-1 and started our study with the aim of determining both the most accurate cut-off value for the vaginal flushing fluid creatinine and the accuracy rate according to this cut-off value. The study included 63 patients. No statistically significant difference was found between the patients whom we considered having PROM or no PROM according to being PAMG-1 positive or negative in terms of mean maternal age, mean gestational weeks, and mean gravidity and parity. There was no statistically significant difference between the mean amniotic fluid indices of the groups. No significant difference in the mean amniotic fluid indices was associated with the fact that all the patients were referred to our clinic either for the complaint of water breaking or the suspicion of oligohydramnios-related water breaking and that the patients had similar characteristics. There was a statistically significant difference in mean values of cervical effacement and cervical dilatation in favor of the PROM patients. The mean values of cervical dilatation and effacement were higher in the PROM group than in the non-PROM group. The reason might be the fact that the patients in this group started preterm labor and that cervical dilatation and effacement could occur in patients with rupture of membranes. In our study, there was no statistically significant relationship between PROM and non-PROM group in terms of time between sampling and delivery. The mean time between sampling and delivery was 14 days and the median value was 1 day in the non-PROM group while the mean time was 27 days and the median value was 21 days in the PROM group.

When compared to the literature, we see that the study conducted by Dale et al. [28]. on 111 PPROM pregnant women between 20-34 weeks found the median value of the latent period to be 7 (0-109) days In our study, we thought that the mean was increased because the post-treatment latent period of two PROM patients were 112 and 80 days after the development of PROM. A statistically significant difference was observed between the vaginal flushing fluid creatinine levels of the PROM and non-PROM patients. In our study, mean creatinine level in vaginal flushing fluid was found to be 0.39 (0.31) mg/dl in the PROM group, and 0.04 (0.10) mg/dl in the non-PROM group. The study performed by Gürbüz et al. [12] also observed the same level to

be 0.026 (0.029) mg/dl in the group whose water did not break, and 0.70 (0.55) mg/dl in the group whose water broke. It has been suggested in previous studies that the creatinine assessment in vaginal flushing fluid can be used as a marker for diagnosis when PROM is clinically suspected in the speculum examination [12,16,19,20,30]. Firstly, the study conducted by Li Hy et al. [29] found that hCG, AFP and creatinine concentrations were high in amniotic fluid. They reported that the assessment of hCG, AFP and creatinine in vaginal flushing fluid was useful. They also stated that creatinine assessment in vaginal flushing fluid is cheaper and easier than hCG and AFP in PROM diagnosis. Secondly, Gürbüz et al. [12] compared the vaginal flushing fluid creatinine levels of 54 pregnant women in whom amnion flow was detected through speculum examinations with the creatinine levels of 34 pregnant women with no complaint. As a result, when the creatinine threshold was taken as 0.12 mg/dl, they observed sensitivity, specificity, positive and negative predictive values to be 100%. The third study on the subject was carried out by Kafalı et al. [19] from Turkey. They assessed the levels of urea and creatinine in vaginal flushing fluid in the PROM diagnosis, and found high levels of urea and creatinine in PROM patients. However, they studied only with the patients whose PROM diagnosis was confirmed with vaginal pooling and nitrazine test. They concluded that sensitivity, specificity, and positive and negative predictive values were all 100% when urea was taken as 12 mg/dl and creatinine as 0.6 mg/dl in vaginal flushing fluid. Based on this result, they argued that urea and creatinine assessment might be used as an easy, cheap and fast test in the PROM diagnosis.

Furthermore, in the study in which Zanjani et al. [20] confirmed PROM diagnosis in the speculum examination according to the presence of pooling and the nitrazine test result, they found 96.5% sensitivity, 100% specificity, 100% positive predictive value and 96.8% negative predictive value when the cut-off value of creatinine in the vaginal flushing fluid was taken as 0.5 mg/dl. However, the high false positivity rate of nitrazine test in the PROM diagnosis due to the possibility of change in vaginal pH in the presence of blood, semen or infection such as bacterial vaginosis has paved the way for other studies.. Sekhavat et al. [16] used fern test and the detection of pooling in the speculum examination to confirm the PROM diagnosis test on the grounds that nitrazine test has a high rate of false positivity. Accordingly, they found 98.7% sensitivity, 100% specificity, 100% positive predictive value and 98.8% negative predictive value when the creatinine cut-off value in the vaginal flushing fluid was taken as 0.14 mg/dl. In our study, the creatinine level in vaginal flushing fluid was calculated with ROC analysis by taking the cut-off value as 0.1050 mg/dl compared to PAMG-1, which is highly accurate in the PROM diagnosis. As a result, 94.4% sensitivity, 93.3% specificity, 85% positive predictive value, and 97.7% negative predictive value were found, and the total diagnostic value was observed to be 93.6%. Unlike other studies, we found a cut-off value of 0.1050 mg/dl for vaginal flushing fluid creatinine. This value was lower than those found in other studies. We attributed this to the higher accuracy of the PAMG-1 test with which we compared creatinine assessment in vaginal flushing fluid for the PROM diagnosis. Limitation of this study is that this research is a retrospective study.

Conclusion

PROM is one of the most troublesome issues in today's obstetrics as one of the most important causes of preterm births. The correct diagnosis of PROM is critical for both maternal and fetal concerns. While a false positive diagnosis leads to unnecessary hospitalization, a false negative diagnosis causes intrauterine infection, increasing morbidity and mortality of both mother and fetus. Therefore, many tests have been performed to confirm the PROM diagnosis. Today, PAMG-1 test is recognized as the most effective and valuable diagnostic method. While there have been attempts to develop several alternative tests, none of them has achieved such success. As shown in our study, we concluded that creatinine assessment in vaginal flushing fluid is a cheaper, faster, easily accessible and highly accurate test in the PROM diagnosis, and we think it might be an alternative to PAMG-1 test.

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Factors affecting mortality in Crimean-Congo hemorrhagic fever

Kırım Kongo kanamalı ateşinde mortaliteyi etkileyen faktörler

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Abstract

Aim: Crimean-Congo hemorrhagic fever is a viral disease that is transmitted by infected ticks and has high mortality. We aim to determine the factors affecting mortality in patients with Crimean–Congo hemorrhagic fever (CCHF).

Methods: Age, gender, number of ticks, tick removal procedures, tick location, time to hospital admission, symptoms, physical examination findings, vital signs, laboratory parameters and factors affecting mortality were evaluated. The study was designed as a retrospective cohort study.

Results: The median age of the 172 patients was 46 (range, 18–78) years, and 73.8% of the patients were men. The mortality rate was high in patients with delayed time to hospital admission, those who were bitten on the head and neck region, those who had a high number of tick bites, those who had removed the tick themselves or had the tick removed by a relative and those who had impaired consciousness (P=0.001, P<0.001, P<0.001, P<0.001 and P=0.002, respectively). Bleeding was detected in 87.2% of cases. The frequency of ecchymosis, pleural effusion, hematuria, hematemesis and melena occurrence was high in non-survivors (P<0.001, P<0.001, P<0.001, P=0.006 and P=0.006, respectively). Fever and heart rate were significantly higher, systolic and diastolic blood pressure was significantly lower in non-survivors (P<0.001, P<0.001, P=0.006 and P<0.001, respectively). Additionally, the white blood cell (WBC) count, international normalized ratio (INR), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly higher and platelet count were significantly lower in non-survivors (P<0.001 for all).

Conclusion: We found that in patients with CCHF, bleeding was a major factor associated with mortality. Factors such as a number of ticks, the number of people removing the ticks and tick location were found to affect mortality. We believe that blood tests and vital parameters can be used to predict mortality in patients with CCHF.

Keywords: Crimean-Congo hemorrhagic fever, Mortality, Emergency department

Öz

Amaç: Kırım kongo kanamalı ateşi enfekte kenelerle bulaşan ve yüksek mortaliteye sahip viral bir hastalıktır. Kırım Kongo Kanamalı Ateşi (KKKA) hastalarında mortalite üzerinde etkili faktörleri belirlemeyi amaçladık.

Yöntemler: Hastaların yaş, cinsiyet, kene teması, kene sayısı, kenenin kim tarafından çıkarıldığı, kenenin vücuttaki lokalizasyonu, hastaneye başvuru süresi, semptomları, fizik muayene ve vital bulguları, laboratuvar parametreleri ve mortaliteye etki eden faktörler değerlendirildi. Çalışma retrospektif kohort olarak dizayn edildi.

Bulgular: 172 hastanın yaş ortancası 46 (18-78) yıl olup, olguların %73,8'i erkekti. Hastaneye başvurusu geç olan, baş ve boyun bölgesinden ısırılmış olan, ısıran kene sayısı fazla olan, keneler kendisi veya yakını tarafından çıkartılan hasaların ve bilinç bozukluğu olan hastaların mortalite sıklığı yüksek saptandı (sırası ile P=0,001, P<0,001, P<0,001, P<0,001, P=0,002). Olguların %87,2'sinde kanama saptandı. Mortal seyreden olgularda ekimoz, akciğerde sıvı, hematüri, hematemez ve melena sıklığı yüksekti (sırası ile P<0,001, P<0,001, P<0,001, P=0,006, P=0,006). Mortal seyreden hastalarda ateş ve kalp hızı anlamlı olarak yüksek; sistolik ve diyastolik kan basınçları ise anlamlı olarak düşük saptandı (sırası ile P<0,001, P<0.001, P=0,006, P<0,001). Mortal seyreden hastalarda beyaz küre (BK) sayısı, uluslararası normalleştirilmiş oran (INR), aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT) düzeyleri anlamlı olarak yüksek, platelet sayısı, anlamlı olarak düşük saptandı (hepsi için P<0,001).

Sonuç: Kanamanın mortalite gelişmesinde temel faktörlerden biri olduğu saptandı. Kene sayısı, çıkartan kişi sayısı ve ısırılma yeri gibi faktörlerin mortalite üzerine etkili olduğu saptandı. Kan tetkikleri ve vital parametrelerin KKKA tanısı olan hastalarda mortal seyredecek hastaların belirlenmesinde kullanılabileceği kanısındayız.

Anahtar kelimeler: Kırım Kongo kanamalı ateşi, Mortalite, Acil servis

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease first described in the 12th century. The causative microorganism is the orthonairovirus from the Nairoviridae family that is carried by ticks in the genus Hyalomma [1,2]. CCHF is endemic to the Balkans, Middle East and Asian regions [1,2]. Although ticks are considered as the principal vector in disease transmission, the transmission of the virus via blood and other body fluids has also been reported [2,3]. Although the pathogenesis of the disease is still unclear, the host immune response, endothelial injury and inflammatory cytokines in infected tissues are believed to play a role in pathogenesis [4].

A CCHF often presents with mild, non-specific findings, but it may also progress to the hemorrhagic stage and result in mortality. The mortality rate associated with this disease is 5%–30%; however, the mortality rate is lower in endemic regions such as Turkey and Russia. It remains unclear whether the differences in mortality are related to regional differences or case management strategies [5,6].

In the present study, we aimed to determine the factors affecting mortality in patients diagnosed with CCHF and contribute to the existing literature.

Materials and methods

The ethical compliance of this study was approved in accordance with the Helsinki Declaration by the Hospital Local Ethics Committee, Ankara, Turkey.

Between January 2014 and January 2019, 1592 patients with tick bites were admitted to our emergency department; 172 patients with the tick bites recorded on the hospital automation system in whom a definitive diagnosis of CCHF. Serum samples taken from patients during the application Jelsa standard tube, Turkey Institute of Public Health, Department of Microbiology Reference Laboratory, and the National Arbovirus Reference and Research on Viral Zoonosis Laboratory was made. The viral RNA extraction assay was performed with the EZ1 Virus Mini Kit (QIAGEN). The real-time PCR analysis was performed with Applied Biosystems, LightCycler® 480 Instrument II (Roche) and Rotor-Gene ™ 3000/6000 (Corbett Research). Patients with a Crimean Congo viral antigen were found to be positive.

Age, gender, number of ticks, tick removal procedure, tick location, time to hospital admission, physical examination findings, vital signs, laboratory parameters and factors affecting mortality were evaluated. Patients aged >18 years with complete records were included in the study, whereas those with bleeding disorders for any reason (hemophilia, gene mutation, etc.), those with trauma-related bleeding signs (ecchymosis, hematoma, etc.) and those with missing records were excluded from the study.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (IBM SPSS 22.0, IBM Corporation, Armonk, NY, USA). Median, minimum and maximum values of quantitative data; in the analysis of qualitative data, frequency, and ratio values were used. Mann-Whitney U test was used for the analysis of quantitative data; the Chi-Squared test was used for the analysis of qualitative independent data and, Fisher's Exact test was used when the Chi-Square test conditions were not provided. The Receiver operating characteristic (ROC) curve was used to calculate the cut-off, sensitivity and specificity values of the data. Logistic regression analysis was used to analyze the factors affecting mortality. $P<0.05$ was considered statistically significant.

Results

The median age of the 172 patients included in the study was 46 (18–78) years, and men comprised 73.8% of patients. The mortality rate was found to be 8.1%. There was no relationship between age, gender and mortality ($P=0.836$ and $P=0.999$, respectively). The mortality rate was found to be significantly higher in patients with delayed admission to the hospital ($P<0.001$). The most common bite localization was the upper extremity, and the mortality rate of head and neck bites was significantly high ($P<0.001$). Although a single tick was detected in 97.7% of patients, the mortality rate was higher in patients with a higher number of tick bites ($P<0.001$). In 97.1% of patients, the tick was removed by the doctor; in these patients, the mortality rate was found to be lower compared with patients in whom the tick was removed by the patient/relatives ($P<0.001$). The most common symptom was fever (72.1%), followed by abdominal pain (40.1%) and diarrhea (34.9%). The mortality rate was higher in patients with impaired consciousness ($P=0.002$). Bleeding was detected in 87.2% of patients. There was no correlation between bleeding and mortality ($P=0.135$). The frequency of ecchymosis, pleural effusion, hematuria, hematemesis and melena occurrence was found to be higher in non-survivors ($P<0.001$, $P<0.001$, $P<0.001$, $P=0.006$ and $P=0.006$, respectively); whereas epistaxis, gingival bleeding and petechiae were not associated with mortality ($P=0.145$, $P=0.137$ and $P=0.293$, respectively). Fever and pulse rate were significantly higher, systolic and diastolic blood pressure was significantly lower in non-survivors ($P<0.001$, $P<0.001$, $P=0.006$ and $P<0.001$, respectively). White blood cell (WBC) counts, international normalized ratio (INR) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly higher and platelet count were significantly lower in non-survivors ($P<0.001$ for all) (Table 1).

ROC analysis results and specificity/sensitivity ratios of WBC count, INR, platelet count, AST and ALT levels, fever, systolic blood pressure, diastolic blood pressure and pulse rate are shown in Figure 1 and Table 2.

A regression analysis performed on non-survivors revealed that none of the factors were predictive of mortality (Table 3).

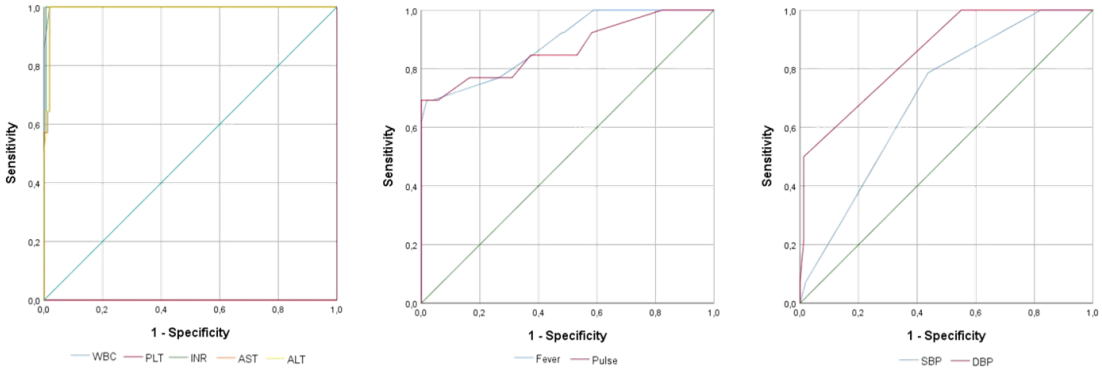

Figure 1: ROC analysis of vital signs and blood values

Table 1: Mortality analysis of influencing factors

		Total (n:172) Median(min-maks)/n(%)	Survival (n:158) Median(min-maks)/n (%)	Non-survivors (n:14) Median(min-maks)/n (%)	*P*-value
Age (years)	46 (18-78)	46 (18-76)	45.5 (21-78)	0.836[α]	
Gender	Male	127 (73.8)	116 (73.4)	11 (78.6)	>0.999[¥]
	Female	45 (26.2)	42 (26.6)	3 (21.4)	
Time to hospital admission (day)	3 (1-9)	3 (1-7)	5 (1-9)	0.001	0.001
Tick location	Head and neck	10 (5.8)	1 (0.6)	9 (64.3)	<0.001[α]
	Body	15 (8.7)	12 (7.6)	3 (21.4)	
	Upper extremity	90 (52.3)	89 (56.3)	1 (7.1)	
	Lower extremity	57 (33.1)	56 (35.4)	1 (7.1)	
Ticks number	1	168 (97.7)	158 (100)	10 (71.4)	<0.001[¥]
	2	4 (2.3)	0	4 (28.6)	
Tick removal	Doctor	167 (97.1)	158 (100)	9 (64.3)	<0.001[¥]
	Patient/relatives	5 (2.9)	0	5 (35.7)	
Symptoms	Fever	124 (72.1)	111 (70.3)	13 (92.9)	0.116[β]
	Subfebrile fever	48 (27.9)	47 (29.7)	1 (7.1)	0.323[¥]
	Abdominal pain	69 (40.1)	63 (39.9)	6 (42.9)	0.827[β]
	Diarrhea	60 (34.9)	55. (34.8)	5. (35.7)	>0.999[¥]
	Muscle/joint pain	30 (17.4)	25. (15.8)	5. (35.7)	0.073[¥]
	Headache	29 (16.9)	26 (13.5)	3 (21.4)	0.708[¥]
	Dizziness Dizziness	28 (16.3)	26 (16.5)	2 (14.3)	<0.999[¥]
	Nausea/vomiting	24 (14)	21 (13.3)	3 (21.4)	0.418[¥]
	Impaired consciousness consciousness	13 (7.6)	8 (5.1)	5 (35.7)	0.002[¥]
	Others*	26 (15.1)	23 (14.6)	3 (21.4)	0.448[¥]
	Bleeding	150 (87.2)	136 (86.1)	14 (100)	0.135[¥]
Symptoms related to bleeding	Ecchymosis	76 (44.2)	63 (39.9)	13 (92.9)	<0.001[¥]
	Epistaxis	67 (39)	59 (37.3)	8 (57.1)	0.145[β]
	Gingival bleeding	31 (18)	26 (16.5)	5 (35.7)	0.137[¥]
	Petechiae	100 (58.1)	90 (57)	10 (71.4)	0.293[¥]
	Pleural effusion	4 (2.3)	0	4 (28.6)	<0.001[¥]
	Hematuria	13 (7.6)	7 (4.4)	6 (42.9)	<0.001[¥]
	Hematemesis	2 (1.2)	0	2 (14.3)	0.006[¥]
	Melena	2 (1.2)	0	2 (14.3)	0.006[¥]
Vital signs	Fever (^{O}C)	38.4 (37.5-40)	38.2 (37.5-39)	39.8 (38.2-40)	<0.001[α]
	SBP (mmHg)	120 (90-150)	120 (90-150)	110 (90-120)	0.009[α]
	DBP (mmHg)	60 (40-75)	60 (50-75)	57.5 (40-60)	<0.001[α]
	Pulse rate (bpm)	80 (76-118)	80 (76-98)	110 (78-118)	<0.001[α]
Laboratory parameters	WBC (x10^{3}/mm^{3})	15 (13-22)	15 (13-19)	20 (19-22)	<0.001[α]
	Platelet (x10^{3}/mm^{3})	89 (40-98)	89 (75-98)	41.5 (40-45)	<0.001[α]
	INR	1.5 (1.3-4.6)	1.5 (1.3-3.9)	4.05 (3.5-4.6)	<0.001[α]
	AST (IU/L)	160 (90-1255)	156 (90-960)	984 (838-1255)	<0.001[α]
	ALT (IU/L)	133 (63-1204)	126 (63-912)	929 (759-1204)	<0.001[α]

α: Mann-Whitney U test, ¥: Fisher' Exact test, β: Chi-Squared test, Others*: sore throat, backache, weakness, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, INR: international normalized ratio, AST: aspartate aminotransferase ALT: alanine aminotransferase

Table 2: Area, cut-off, sensitivity and specificity of vital signs and blood values

Variable (s)	Area				Asymptotic 95% CI	
		Cut-off	Sensitivity	Specificity	Lower Bound	Upper Bound
WBC (x10^{3}/mm^{3})	0.999	18500	100	98.1	0.996	1.000
Platelet (x10^{3}/mm^{3})	>0.999	60000	100	100	1.000	1.000
INR	0.997	2.75	100	99.4	0.992	1.000
AST (IU/L)	0.992	682	100	98.1	0.982	1.000
ALT (IU/L)	0.993	607.5	100	98.1	0.983	1.000
Fever (^{O}C)	0.888	38.7	69.2	96.2	0.785	0.991
SBP (mmHg)	0.701	115	78.6	56.3	0.579	0.823
DBP (mmHg)	0.855	52.5	78.6	98.7	0.758	0.951
Pulse rate (bpm)	0.868	82.5	84.6	61.4	0.054	0.257

CI: Confidence Interval, WBC: white blood cell, INR: international normalized ratio, AST: aspartate aminotransferase ALT: alanine aminotransferase, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 3: Logistic regression analysis of factors affecting mortality

	B	S.E.	Wald	*P*-value	Odds ratio
Tick location	-2.475	6830.711	0.000	1.000	0.084
Time to hospital admission (day)	0.126	3774.177	0.000	1.000	1.134
Number of ticks	-0.492	38032.052	0.000	1.000	0.612
Tick removal	-6.024	42157.078	0.000	1.000	0.002
Pleural effusion	1.522	44221.525	0.000	1.000	4.580
Hematemesis	-2.617	68776.325	0.000	1.000	0.073
Fever (^{O}C)	0.634	10838.984	0.000	1.000	1.885
SBP (mmHg)	0.023	414.191	0.000	1.000	1.023
DBP (mmHg)	0.007	908.723	0.000	1.000	1.007
Pulse rate (bpm)	0.052	650.395	0.000	1.000	1.054
WBC (x10^{3}/mm^{3})	0.001	4.271	0.000	1.000	1.001
Platelet (x10^{3}/mm^{3})	-0.001	0.683	0.000	0.999	0.999
INR	2.313	8035.493	0.000	1.000	10.106
AST (IU/L)	0.041	186.557	0.000	1.000	1.042
ALT (IU/L)	-0.040	188.781	0.000	1.000	0.961
Impaired consciousness	-1.430	15969.314	0.000	1.000	0.239
Ecchymosis	-0.783	10005.927	0.000	1.000	0.457
Melena	5.792	55499.290	0.000	1.000	327.655
Hematuria	-2.575	12429.540	0.000	1.000	0.076
Constant	-14.249	531592.665	0.000	1.000	0.000

B: regression coefficient, S.E.: Standard error of the coefficient, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, INR: international normalized ratio, AST: aspartate aminotransferase ALT: alanine aminotransferase

Discussion

CCHF symptoms are observed only in human hosts. The disease progresses along four stages: incubation, pre-hemorrhagic stage, hemorrhagic stage and healing stage [2]. The increased viral load in the liver and lymphoid tissues gradually leads to coagulopathy, subsequently leading to thrombocytopenia, organ failure and shock [7]. The disease severity is associated with the viral load and severity of bleeding [2,8]. Furthermore, it has been reported that CCHF can lead to organ failure by causing apoptosis in many cell types of endothelial and parenchymal origin [4].

Saksida et al. [9], Hasanoğlu et al. [7] and Yilmaz et al. [10] reported the mortality rate associated with CCHF to be 27.5%, 8.1%, and 5%, respectively. The mortality rate was reported to be lower in countries such as Turkey and Russia, where CCHF is endemic, but the underlying reasons have not yet been elucidated [5,6]. In agreement with findings in the literature, the mortality rate was found to be 8.1% in the present study. We believe that differences in vector, host or pathogen structure and/or administered treatments result in different mortality rates.

Studies have shown that the disease occurs in all age groups and is more common in men [7,11]. The proportion of male patients in the present study was consistent with previous findings, and no relationship was found between age, gender and mortality. We believe that all age groups are at similar risk because although the elderly and children do not actively work in Turkey, they visit rural or forested areas together with their families where they come in close contact with animals that carry ticks. The frequency of tick contact is higher in men because they work in fields and forested lands, whereas women usually perform household chores.

The incubation period begins after viral infection and lasts 3–7 days. Symptoms are not expected to manifest during this period. The pre-hemorrhagic stage begins after the incubation period and lasts 4–5 days, followed by the hemorrhagic stage, during which the patient develops bleeding-related symptoms [2,12]. In the present study, it was found that patients began to exhibit symptoms three days after tick removal, and non-survivors had a delayed admission to the emergency department. We believe that the patients did not present to the emergency department before three days because of the lack of any symptoms during the incubation period, and because they ignored the symptoms that occurred during the pre-hemorrhagic period. We believe that the non-survivors ignored the symptoms prior to the disease entering the hemorrhagic stage and attributed

their non-specific findings to other causes. Therefore, we attribute some of the patients' death to their inability to combat increased viral loads, bleeding, sepsis and shock. Some studies reported that fever observed during the pre-hemorrhagic period was the most common symptom, followed by asthenia, headache, anorexia and myalgia [7,10,12]. During the pre-hemorrhagic period, fever rises suddenly and can reach 40°C [12]. Hasanoğlu et al. [7] reported no relationship between high fever and mortality. Ahmeti et al. [1] reported that non-specific findings did not affect the clinical course of patients. In the present study, the most common symptom was fever, followed by abdominal pain and diarrhea. There was no relationship between non-specific findings and mortality. We found that patients who presented with impaired consciousness had a higher mortality rate. We believe that cytokines and interleukins secreted as a result of inflammation against the virus in the pre-hemorrhagic stage of infection are responsible for these symptoms. We believe that these symptoms are not associated with mortality because of the low viral load in the pre-hemorrhagic stage and no bleeding incidence. Furthermore, the cause of impaired consciousness may be secondary to sepsis or hemorrhagic shock, or it may be caused by minor intracranial hemorrhages that are not observed on imaging findings. Therefore, these patients have a higher mortality rate.

The hemorrhagic stage of CCHF results in either recovery or death. Bradycardia and hypotension may develop during this period because of sepsis, septic shock and hemorrhage [12]. Ahmeti et al. [1] reported that bradycardia and blood pressure played no role in determining the clinical course. In the present study, fever and heart rate were found to be higher and blood pressure was found to be lower in non-survivors. We believe that increases in fever and heart rate and decrease in blood pressure are a result of the elevated inflammation in response to the viral load and occurrence of superinfections and shock caused by sepsis and hemorrhage.

Previous studies reported that tick bites generally occur on the torso and extremities [11,13]. Uluğ et al. [11] reported that 74% of ticks were removed by a doctor and that fragmented tick tissues remained in cases where the ticks were removed by the patient or his/her relatives. They also reported more than one tick in 3% of the cases. Similar to findings in the literature, in the present study, the most frequent bite location was the torso and arms; more than one tick was present in 2.3% of the cases, and the tick was removed by the patient or his/her relatives in 2.3% of the cases. We found that the mortality rate was higher in cases in which the bite was located in the head and neck region, there was more than one bite, and the tick was not removed by a doctor. We believe that the torso and extremities are frequently bitten because of their large surface area, and because some patients are engaged in farm work, resulting in a higher frequency of tick contact, and because some patients use traditional treatment methods instead of visiting a doctor. We believe that mortality is higher in cases of tick bites in the head and neck region owing to higher blood circulation in this region. Additionally, mortality is higher in cases with more than one tick bite owing to higher viral load and a higher risk of contracting CCHF. Mortality is also higher in cases in which the tick is not removed by a healthcare professional because tick tissues may remain on the skin and tick saliva may enter the body in cases where the tick is squeezed during removal.

The main cause of bleeding in CCHF is endothelial damage, decreased production of coagulation factors in the liver, and destruction of blood cells [4]. The tendency for bleeding increases in patients with CCHF and extensive bleeding occurs especially in subcutaneous tissues; additionally, epistaxis, gingival bleeding, hematuria, hematemesis, vaginal bleeding and bleeding occur in internal organs [3,14,15]. Gök et al. [12] reported that hematuria, hematemesis, hematochezia, melena and vaginal bleeding were common findings in patients with CCHF, and bleeding in the lungs, brain and peritoneum were rarely observed. Saksida et al. [9] reported bleeding in all patients with a severe clinical course or fatal outcome. Hasanoğlu et al. [7] reported that 25% of cases had bleeding and emphasized that bleeding was as important as the viral load for mortality. They also reported that patients who developed petechiae, melena, epistaxis and hematuria had a higher mortality rate. Ahmeti et al. [1] reported that patients with bleeding had a poor clinical picture. In the present study, we found that bleeding occurred in 87.1% of the cases and the risk of mortality increased in cases with bleeding in regions with high blood loss, such as the lungs, intestinal system and bladder. We believe that the frequency of bleeding increases in patients with CCHF because of impairment or decreased production of coagulation factors and thrombocytopenia. We believe that hemorrhagic shock develops as a result of hemorrhage in patients with CCHF and deteriorated hemodynamics increases mortality.

Because there is no effective vaccine or treatment for CCHF, Bartolini et al. [16] emphasized the importance of laboratory analysis in the detection of CCHF outbreaks, in monitoring patients with fever of unknown causes and in the evaluation of the clinical status of patients.

Yılmaz et al. [10] reported that thrombocytopenia and leukopenia are among the primary laboratory findings of CCHF and that thrombocytopenia developed in 93.2% of cases and leukopenia developed in 88.9% of cases. Hasanoglu et al. [7] found that platelet and leukocyte counts were significantly lower in non-survivors but the WBC count was not significant in predicting mortality. Ahmeti et al. [1] reported that patients with a leukocyte count higher than 7700/μL had a poor clinical status and thrombocyte count was not associated with the clinical status. Swanepoel et al. [17] reported that WBC counts higher than 10,000/mm3 and/or platelet counts lower than 20000/mm3 were associated with poor prognosis. In the present study, thrombocytopenia and elevation in WBC counts were observed in non-survivors. We believe that decreased platelet counts occur due to deterioration of cell structure. We believe that sepsis and increased viral load leads to increased WBC counts, increased platelet destructions and decreased platelet production due to organ failure.

Yılmaz et al. [10] reported elevated transaminase levels in 85.9% of patients with CCHF. Hasanoğlu et al. [7] reported that transaminase levels and INR values were increased further in non-survivors. Ahmeti et al. [1] reported that AST, ALT and thrombocytopenia played no role in determining the clinical status; however, they used low cut-off values for ALS and ALT (168 U/mL and 147 U/mL, respectively). Saksida et al. [9]

reported that transaminase levels of non-survivors were higher and their partial thromboplastin time was longer. Swanepoel et al. [17] reported that AST and ALT levels above 200 U/L and 150 U/L, respectively, indicated poor prognosis. Consistent with findings in the literature, in our study, INR was prolonged and AST and ALT levels were high. We believe that excessive viral loads and sepsis cause more cell damage and apoptosis in the liver, and therefore, INR and AST and ALT levels are higher in non-survivors.

Hasanoğlu et al. [7] found that AST had a specificity of 87% and sensitivity of 79%, ALT had a specificity of 91% and sensitivity of 71%, platelet count had a specificity of 61% and sensitivity of 86% and INR had a specificity of 81% and sensitivity of 93% for predicting prognosis. In our study, the sensitivity was 100% and specificity was 98.1%–100% for the determined cut-off values. The high sensitivity and specificity of AST, ALT and INR levels above the determined cut-off values in the blood tests and platelet count below the determined cut-off value may be indicative of mortality in these patients.

To our knowledge, there is no study in the literature evaluating the sensitivity and specificity of vital parameters for CCHF. For vital parameters, the sensitivity was 69.2%–84.6% and specificity was 56.3%–96.2%. We believe that vital parameters can be used to predict mortality in patients with CCHF.

Our study has several limitations. First, this study is a single-center, retrospective study. Second, the number of patients in study groups is small at some level. Further large-scale, multicenter studies are needed.

Conclusion

The occurrence of bleeding in some regions is one of the main factors for mortality. Factors such as the number of ticks, the number of people removing the ticks and location of the bite were found to affect mortality. We believe that blood tests and vital parameters can be used to predict mortality in patients with CCHF.

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Comparing the effects of silver sulfadiazine and cerium nitrate silver sulfadiazine on burn-wound healing and survival rate of rat animal model

Gümüş sülfadiazin ve seryum nitrat gümüş sülfadiazin'in yanık yarası iyileşmesi ve sıçan hayvan modelinde sağkalım oranı üzerindeki etkilerinin karşılaştırılması

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Abstract

Aim: Current studies about burn therapy are focusing on survival rate of patients with severe burned. So, here we aim to assess the effects of cerium nitrate silver sulfadiazine (CN+SSD) and compare with SSD ointment on mortality and burn healing in rat animal model.

Methods: Twenty rats were used in this study. After inducing burn wounds on back skin of animals, they were classified into two groups randomly. In one group, SSD was administrated topically immediately after inducing burn wound and in the other the combination of CN+SSD was applied. The treatments in both groups were continued as administration of the ointments two times per day for 28 days. Animal's weight and wound sizes were measured 7, 14, 21 and 28 days after burn induction in all animals. The mortality of rats as well as their wound histopathology was also evaluated.

Results: On day 28, wound's average size was decreased to 25 and 27% of initial area in SSD and CN +SSD groups, respectively. In CN+SSD group, the wound size was not smaller than SSD group significantly. Histological comparison has demonstrated no significant differences between CN+SSD group and SSD treated.

Conclusion: The results of our study did not show any differences between CN+SSD and SSD topical treatments in terms of wound healing and mortality rate in rat animal model significantly.

Keywords: Skin-burn, Cerium nitrate silver sulfadiazine, Wound-healing, Mortality, Animal model

Öz

Amaç: Yanık tedavisi ile ilgili güncel çalışmalar, ciddi yanık hastalarının hayatta kalma oranlarına odaklanmaktadır. Bu nedenle, burada seryum nitrat gümüş sülfadiazin (CN+SSD) etkilerini değerlendirmeyi ve sıçan hayvan modelinde SSD merhem ile mortalite ve yanık iyileşmesi arasındaki karşılaştırmayı hedefledik.

Yöntemler: Bu çalışmada 20 rat kullanıldı. Hayvanların arka derisinde yanık yaraları indüklendikten sonra rastgele iki gruba ayrıldı. Bir grupta SSD, yanık yarasının indüklenmesinden hemen sonra topikal olarak uygulandı ve diğerinde CN+SSD'nin kombinasyonu uygulandı. Her iki grupta da, merhemlerin 28 gün boyunca günde iki kez uygulanmasına devam edildi. Animalin ağırlık ve yara ebatları, bütün hayvanlarda yanma indüksiyonundan 7, 14, 21 ve 28 gün sonra ölçüldü. Sıçanlardaki ölümlerin yanı sıra yara histopatolojileri de değerlendirildi.

Bulgular: 28. günde, yaranın ortalama büyüklüğü sırasıyla SSD ve CN+SSD gruplarında başlangıçtaki alanın %25 ve %27'sine düşürüldü. CN+SSD grubunda yara büyüklüğü SSD grubundan anlamlı derecede küçük değildi. Histolojik karşılaştırma, CN+SSD grubu ile tedavi edilen SSD arasında anlamlı bir fark olmadığını göstermiştir.

Sonuç: Çalışmamızın sonuçları, sıçan hayvan modelinde CN+SSD ve SSD topikal tedavileri arasında yara iyileşmesi ve mortalite oranı açısından anlamlı bir farklılık göstermedi.

Anahtar kelimeler: Deri yanığı, Seryum nitrat gümüş sülfadiazin, Yara iyileşmesi, Mortalite, Hayvan modeli

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Introduction

The new classification of skin burns are including erythema involving merely epidermis (first degree), the epidermis and upper dermis involvement as a superficial thickness and deep partial thickness (both as a second degree), epidermis and dermis involvement with full thickness (as a third degree) and also appendages [1]. Massive burns constitute remarkable complications including mortality and morbidity [2,3]. Burns related-mortalities are classified in early and late deaths. The circulatory shock can cause early mortality [4] which happens in extensive burns and/or acute respiratory failures following inhalational damages [5]. Late deaths are typically attributing to sepsis [6]; however, recent studies have identified that these type of death after burn might be due to immune failure in the lack of documented sepsis [7].

Current studies about burn therapy are focusing on survival rate of patients affecting more than half of their total body surface [8]. The main cause of death in severe burned patients is septic problems. Silver sulfadiazine as a topical antibacterial agent has reduced the risk of septic events but the appearance of resistant strains has restrained the efficacy of them. Silver sulfadiazine ointment has been extensively applied in topical case of burns [7]. However, there is a high failure rate while deep burns exceed 60 percent of body surface. Using silver sulfadiazine ointment in combination with cerium nitrate elevates the rate of healing up to 2.2 fold in large or massive burns cases [7,9].

The best way for preventing the infections covering the extensive burns is just by applying autologous skins which results in definitive covering; nevertheless, healthy skin areas are generally not sufficient to achieve this [8]. Homograft can solve the problem of wound healing temporarily, but in the case of applying both auto graft and homograft, there is the necessity to remove the necrosis tissue before employing the grafts. The postoperative complications including bleeding and risk of infection can limit the excised wound area [1].

Monafo et al. in 1976 proposed that extensive burns can be treated by topical CN as an antiseptic agent [10]. Single applying of cerium nitrate has changed the Gram-negative frequency to the Gram-positive species in the wounds. It can use with silver sulfadiazine (CN+SSD) to diminish burns bacterial contamination. Also, they are used to improve the burn patients' prognosis, particularly in severe cases [11,12]. CN+SSD administration changes the burn eschars' appearance and simulate bound tightly for some months [7]. During clinical studies, no toxic reaction has happened except transient and temperate cases of leucopenia. In these cases leucopenia has induced by silver sulfadiazine, and methemoglobinemia [7,13].

Although primary studies revealed encouraging results [14], there are few studies of using topical CN+SSD to burn care, as well as some reports which demonstrate no differences between therapeutic effects of single silver sulfadiazine (SSD) [15] and combination of (CN+SSD) significantly [7,16,17]. Therefore, to clarify and compare the therapeutic role of CN and SSD, herein, a controlled experimental study on rat burn animal model has conducted.

Materials and methods

This study was performed based on the animal research guidelines (National Institutes of Health). Our study was approved by Iran University of medical sciences' ethic committee.

Animals

Twenty male Wistar rats aged six to eight months (approximately 200–250 gr) were used in our experiment. They were put in plastic cages with food and water ad libitum. With a 12-h light and dark cycle and the temperature was controlled.

Anesthesia

They were anesthetized using single intramuscular xylazine and ketamine hydrochloride injections (6 mg/kg and 85 mg/kg, respectively).

Thermal injury

After anesthetizing the rats, they were shaved and ready with 70% ethanol solution. Then, the skin burns model of full-thickness second-degree by using steel probes, were prepared in a 3.5 cm^2 surface area (about 20% of the whole rat skin surface). For reaching to the thermal equilibrium, the probe was immersed (by boiling in100 °C water). Then, without any pressure the probe was put on the shaved back part of the rats (20 seconds). After that, the animals were immediately resuscitated by using intraperitoneal solution of lactated ringer with dose of 2 ml per 100 g body weight.

Animal experiments

After inducing thermal injury, they were classified into two similar groups randomly (10 animals each). In the first group (SSD group), burned areas were covered with SSD ointment which contains Silverdin, Deva and Silver sulfadiazine with dosage of 10 mg per gram, immediately after burning and twice a day for 4 weeks. The burned areas in the second group (CN+SSD group) were covered immediately after burn with CN+SSD ointment and then twice a day for 4 weeks.

Wound healing and mortality rate follow-up

Regarding to trace the wound healing process, the lesions' sizes (in cm^2) were measured at 7, 14, 21 and 28 days' intervals. Seven days after the burn injury induction, wound area was considered 100% and was compared on the day of injury and on the subsequent days. The rate of mortality was determined at 28 days after burn injury in each experimental group. The animals were weighed at 7, 14, 21 and 28 days during the study.

Histopathological examination

In 2 different time point -14 and 28 days after thermal induction- the samples of small excisions containing part of the wounded area were used for histological evaluations. They were fixed by formalin 10% and preparing the sections which embedded by paraffin and using microtome (5-µm thick) were performed. The prepared tissue sections were stained by H&E (Hematoxylin & Eosin) and also Masson's trichrome for light microscopy examination. The average number of inflammatory cells (×400 magnification) in healed area can determine the severity of inflammation in each group.

Statistical analysis

The data have been reported as means (standard deviation). Statistical differences in two groups (SSD &

CN+SSD) were calculated using T-test. The statistical analyses were done using GraphPad Prism software version 6.01. *P*-value less than 0.05 was considered as statistically significant.

Results

Average weight of animals in SSD and CN+SSD groups were 218 (29) and 221 (26) grams, before beginning of this study, respectively. 7 days after induction of burn injury, the weight of rats in SSD and CN+SSD groups was decreased to 201 and 205 grams, respectively. No significant difference was reported between groups in terms of animal weights during follow-up. At the end of 28-day treatment, the slightly increased in average weight of animals was shown (Table 1).

Two rats died four days after burn induction (one in each group), therefore, no significant difference was reported in mortality rate between SSD group and CN+SSD treatment group.

The surface area of skin lesions was measured in 7, 14, 21 and 28 days after induction of injury. The reduction rate was calculated in comparison with wound size in 7th day. The mean of wound size after 28 days was decreased to 25 and 27 percent of the burned area in 7th day in SSD and CN+SSD groups, respectively (Table 2). No statistical difference was reported between these two groups (P=0.094). Also in terms of wound size on the 28th day of treatment no statistical difference was reported among SSD and CN+SSD groups. The representative image of induced burned areas, 28 days after initiating the treatments is presented in Figure 1.

Histological studies' results demonstrated the wound healing improvement 28th day after treatment. The samples from SSD and CN+SSD treated wounds showed complete inflammatory cell infiltration, epidermis re-epithelialization and dermis fibrosis.

Table 1: Body weights of rats treated with SSD and CN+SSD ointments before and during 7 days after induction of burn injury

Body weights (g)	SSD Group	CN+SSD Group
Before the study	218 g	221 g
Day 7	201 g	205 g
Day 14	198 g	200 g
Day 21	200 g	204 g
Day 28	205 g	211 g

Table 2: Comparison of wound burn size in SSD and CN+SSD treated rats

Wound burn size (mm^2)	SSD Group	CN+SSD Group
Day 7	100%	100%
Day 14	33%	37%
Day 21	29%	32%
Day 28	25%	27%

The wound size area was stated as 100% on the 7th day and the ratio of wound size in following days to 7th day was calculated.

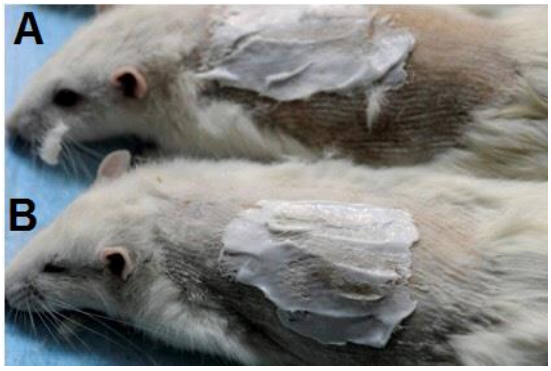

Figure 1: Induced skin burns on rats that treated with SSD (A) and CN+SSD (B) Ointments after 28 days

Discussion

In this animal study, we assessed the effects of SSD and CN+SSD on healing of burn wounds in animal model and compared the results. Generally, our results showed that there is no significant difference between SSD and CN+SSD in terms of enhancing wound healing process and survival rate of rats.

In a prospective investigation which has been done multicenter, has been shown that Ce-SSD was approved but experiments were finished in 2000s incompletely [18]. Ce-SSD is extensively applied in Europe (Flammacerium®) but in the United States and United Kingdom, just was used for the treatment of infrequent diseases [10].

Reduction of 46 percent in deaths following use of CN+SSD has been reported [19]; but these results have been opposed in past years while topical CN or SSD was applied. Previous studies showed that for the treatment of acute facial burns there is no significant difference between CN+SSD or SSD [9]. In burned mice and rats, the effectiveness of CN+SSD in bacterial infection and mortality inhibition has been reported [7,10]. Animals which have been treated with zinc sulfadiazine displayed better and quicker wound healing. Unlike silver and zinc SD, the cerium SD can create an insoluble complex of cerium-DNA [18]. Cerium SD toxicity is less than zinc or silver SD [18]. Both the silver SD's effectiveness and potential wound-healing capacity of zinc SD accompanied by cerium SD's low toxicity could be merge to generate the best topical treatment [20]. In some animal burns studies, CN inhibited death [21], and improved the cellular immunity. It has not been reported with sulfamylon, silver nitrate or SSD [22,23]. The results of this investigation show that infectious organisms are not the only cause of immune suppression induction. In the skin, CN binds to a toxic lipid protein complex manufactured by heat [21]. It can suppress the immunologic responses through the mitochondria and cell membrane [24] and ruffles metabolic function [25].

On the other hand, in a one-year prospective study, CN+SSD ointment (Flammacerium®) was used for a group of children (N=47). They have second to third-degree thermal injuries with five to 60 percent of body surface involvement. They showed the good to very good therapeutic results at the end of study [26].

The effect of CN+SSD ointment was assessed in compare to SSD cream in a randomized study of 60 massive burns patients. In this study none of the treatments have superiority over the other one [17].

Some results showed that there is no inhibition or decreasing in bacterial growth in severe injuries covering more than 50 to 60% of total body surface area by using SSD. First experiments introduced that CN as an inexpensive agent with low toxicity had a wide antibacterial and antifungal spectrum. Applying in burns by wet compresses or using a water soluble cream, the CN merely showed Gram-negative organisms inhibition; but SSD specially prevents Gram-positive one [12]. The clinical trials of administration of topical treatments including combined CN with SSD reported reduced mortality rate up to 50% [11]. But, in two controlled studies applying SSD–CN and single SSD, no significant difference in terms of mortality rate and wound flora modulation was seen between two

treatments [16]. The results of other study which was performed in adults, the results were introduced no difference between SSD and SSD–CN [17].

Collectively, these data along with our finding from SSD and CN+SSD groups showed no statistical difference between applying CN+SSD and single SSD in terms of enhancing wound healing process and survival rate of rats. Based on our finding, future studies are recommended.

Conclusion

In conclusion, the results of our study did not show any significant differences in wound healing and mortality rate between CN+SSD and SSD topical treatment in rat animal model.

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Is insulin resistance associated with fatigue, the severity of the disease and motor disability in idiopathic Parkinson's disease?

İdiopatik Parkinson hastalığında insülin direnci yorgunluk, hastalık şiddeti ve motor yetersizlik ile ilişkili midir?

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Abstract

Aim: Abnormal glucose metabolism is known to potentially correlate abnormal mitochondrial function and neurodegenerative processes. The purpose of the study was to determine the association of insulin resistance on fatigue, the severity of the disease and motor disability in patients with idiopathic Parkinson's disease (IPD).

Methods: A total of 50 patients diagnosed with IPD by a neurologist from university hospital were enrolled to study. Demographic characteristics (age, gender, height, weight and body mass index (BMI) were recorded. Patients were allocated into two groups by insulin resistance (IR), named insulin resistance (+) as group 1 (IR+) (n=30 (10 female, 20 male), age=66 years, height=169 cm, weight=75 kg, BMI=26.6 kg/m^2 (median)) and insulin resistance (-) as group 2 (IR-) (n=20 (8 female, 12 male), age=63.5 years, height=168 cm, weight=75 kg, BMI=26.95 kg/m^2 (median)). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test was used for assessment of insulin resistance. The disease severity was assessed by the Modified Hoehn and Yahr Scale, motor disability was assessed by Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) and fatigue was rated by Fatigue Severity Scale (FSS).

Results: MDS-UPDRS scores were statistically significantly different between the groups of IPD patients with IR (+) and IR (-) (P=0.034). Modified Hoehn - Yahr (P=0.300) and FSS (P=0.147) scores were not statistically significantly different between the same groups.

Conclusion: This study suggests that IR may have a role for disease severity in patients with IPD. In patients with IPD, insulin resistance should be questioned and considered in the treatment and rehabilitation program.

Keywords: Idiopathic Parkinson's disease, Insulin resistance, Fatigue, Motor disability

Öz

Amaç: Anormal glukoz metabolizmasının, anormal mitokondriyal fonksiyon ve nörodejeneratif süreçler ile potansiyel olarak ilişkili olduğu bilinmektedir. Çalışmanın amacı idiopatik Parkinson hastalığı (İPH) olan hastalarda insulin direnci ile yorgunluk, hastalık şiddeti ve motor yetersizlik ile ilişkisini incelemektir.

Yöntemler: Çalışmaya üniversite hastanesine başvuran ve nörolog tarafından İPH tanısı alan toplam 50 hasta alındı. Hastaların demografik özellikleri (yaş, cinsiyet, boy, kilo, vücut kitle indeksi (VKİ) kaydedildi. Hastalar insulin direnci (IR) olup olmamasına göre iki gruba ayrıldı. İnsülin direnci olan grup, grup 1 (IR+) (n=30 (10 kadın, 20 erkek, yaş= 66, boy=169 cm, kilo=75 kg, VKI=26,6 kg/m2 (medyan)), insulin direnci olmayan grup, grup 2 (IR-) (n=20 (8 kadın, 12 erkek, yaş=63,5, boy=168 cm, kilo=75 kg, VKI=26,95 kg/m2 (medyan)). İnsülin direncinin değerlendirilmesi için Homeostatic Model of Assessment-Insulin Resistance (HOMA-IR) testi yapıldı. Hastalık şiddeti Modified Hoehn-Yahr skalası ile, motor yetersizlik Birleşik Parkinson Hastalığı Derecelendirme Ölçeği (MDS-UPDRS) skalası ile, yorgunluk ise Yorgunluk Etki Ölçeği ile değerlendirildi.

Bulgular: MDS-UPDRS skorları IR (+) ve IR (-) olan İPH hasta grupları arasında istatistiksel olarak anlamlı farklılık gösterdi (P=0,034). Modifiye Hoehn - Yahr (P=0,300) ve FSS (P=0,147) skorları açısından gruplar arasında istatistiksel olarak anlamlı farklılık bulunmadı.

Sonuç: Bu çalışma, İPH hastalarında IR'nin hastalık şiddeti için bir rolü olabileceğini düşündürmektedir. İPH'li hastalarda insülin direnci sorgulanmalı ve tedavi ve rehabilitasyon programında düşünülmelidir.

Anahtar kelimeler: İdiopatik Parkinson hastalığı, İnsülin direnci, Yorgunluk, Motor yetersizlik

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Introduction

Idiopathic Parkinson's disease (IPD) is the most common age-related movement disorder associated with neurodegenerative disease. IPD is characterized by bradykinesia, resting tremor, rigidity and motor symptoms of postural instability at the advanced stage. Also nowadays it is known that psychiatric disorders including dementia, depression and anxiety, autonomic disorders such as sleep disturbances, orthostatic hypotension, abnormal thermoregulation and urinary problems, blurry vision caused by impaired accommodation, olfactory disorders, dysphasia, craniofacial disorders such as sialorrhea and non-motor symptoms like fatigue may also occur before and during the disease. Non-motor symptoms as well as motor symptoms contribute to the morbidity associated with disease. Fatigue is a non-motor symptom that occurs in nearly 50% of IPD sufferers [1].

Alterations in endocrine functions and low-grade systemic inflammation are the main drivers of insulin resistance. Several research studies in epidemiology, molecular genetics and cell biology have identified relations between Parkinson's disease and insulin resistance. Recent studies have showed common cellular pathways that potentially relate neurodegenerative processes with abnormal mitochondrial function and abnormal glucose metabolism. This evidence defining that peroxisome proliferator activated receptor gamma coactivator 1-α, a key regulator of enzymes involved in mitochondrial respiration and insulin resistance, is potentially very important in the pathogenesis of neurodegeneration in Parkinson's disease [2]. These biological systems have also been linked to fatigue symptoms. Importantly, inflammation is associated with substantial changes in the biosynthesis of monoamines including dopamine, noradrenaline and serotonin which are involved in the pathophysiology of fatigue symptoms. We know that in PD, dopaminergic midbrain neurons degenerate, cause to cerebral dopamine decrease.

Review of the relevant literature clearly shows that there is a need to identify the exact role of these pathways and to what extent insulin resistance plays a role in the development of fatigue, the severity of the disease and motor disability in IPD.

The mechanism underlying fatigue development in insulin resistance is considered to involve endocrine/metabolic and inflammatory processes [3]. Therefore, the association of fatigue with insulin resistance in IPD patients is examined in the current study with the aim to support this consideration.

Materials and methods

Study design and subjects

A cross-sectional observational study enrolled patients diagnosed with IPD who were being followed at the Neurology outpatient clinics at SANKO University Research and Practice Hospital. The patients were consecutively included in the study by the same Neurologist.

IPD diagnosis was confirmed using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [4].

As a result of the power analysis with 80% effect size with 0.05 error margin, total sample size was determined as 42 patients.

A total of 50 patients (32 males, 18 females) without a diagnosis of dementia or any neurological and/or systemic disorders that could cause fatigue were enrolled in the study. Individuals with a psychiatric illness that could interfere with the ability to accurately understand and complete the questionnaire were excluded as were those being treated with neuroleptic drugs and antidepressants (Figure 1). Demographic characteristics of all participants were recorded. Age, gender, marital status, education level, known comorbidities, duration of IPD, initial motor symptoms, anti-Parkinson medications taken and clinical findings were recorded through face-to-face communication with patients.

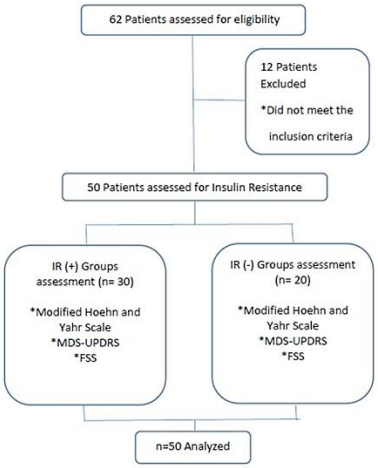

Figure 1: Flowchart of the study

Metabolic analysis

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test was performed for measurement of insulin resistance. The body weight, height and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) were recorded for all patients. Blood samples were obtained and centrifuged at room temperature for 5 minutes at 3000 RPM. Extracted sera were kept in ice bags and transferred to deep freezers for storage at -80°C on the same day. Blood samples obtained after 8-10 hours of fasting were used for HOMA-IR test. For this test, fasting blood glucose and fasting insulin values were multiplied and the product was divided by 405. A cut-off value of 2.5 was chosen for the test. Insulin resistance was considered positive if the test result was greater than 2.5 [5].

Enrolled patients were divided into two groups, according to their insulin resistance: Group 1; IR(+): 30 IPD patients with insulin resistance by HOMA-IR test, Group 2; IR(-): 20 IPD patients without insulin resistance by HOMA-IR test.

Clinical assessment

The disease severity was assessed by the Modified Hoehn and Yahr Scale. The Hoehn and Yahr scale is used to describe the severity Parkinson disease. The scale was originally described in 1967 and had 5 stages, 1 to 5. It has since been modified with the addition of stages 1.5 and 2.5 to account for the intermediate course of Parkinson disease [6]. 1 means: Unilateral involvement only and symptoms are mild. 5 means: Wheelchair bound or bedridden unless aided.

Motor disability was assessed with Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) [7]. The scale is considered to be the gold standard since it provides comprehensive information in many directions between the

clinical measures used in the evaluation. Scale includes 4 parts, respectively; Part I: Nonmotor Aspects of Experiences of Daily Living, Part II: Motor Experiences of Daily Living, Part III: Motor Examination, Part IV: Motor Complications. The sum of the scores of the first 3 parts gives a total score. Low scores reflect less disability.

Fatigue assessment

Fatigue was rated using the Fatigue Severity Scale (FSS). The FSS, which was published in 1989 by Krupp, has 9 items. For each question, the patient is asked to choose a number from 1 to 7 that indicates how much the patient agrees with each statement, where 1 indicates strong disagreement and 7 indicates strong agreement. A score of 4 or higher generally indicates severe fatigue [8].

The study was approved by the SANKO University Ethics Committee for Clinical Research Trials (2018/04;14. 19.04.2018) and conducted in accordance with the principles set forth in the Declaration of Helsinki. All participants gave their written informed consent before their participation in the study and were free to withdraw at any time.

Statistical analysis

IBM SPSS 24 package program was used for statistical analyses (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as median (minimum–maximum), number and percentage. Normality of data was evaluated with Shapiro-Wilk test. Mann-Whitney U test was used for comparing of two groups' MDS-UPDRS, Modified Hoehn-Yahr and FSS values. For all analyses $P<0.05$ was considered statistically significant.

Results

Demographic features

In this study 50 IPD patients, 30 (60%) were insulin resistance-positive (IR+) of whom 10 (33.3%) were females and 20 (66.7%) were males, the remaining 20 patients (40%) did not show insulin resistance (IR-), of whom 8 (40%) were females, 12 (60%) were males. Table 1 shows the demographic characteristics of groups. There was no statistically significant difference between the two groups with respect to body weight, height or age distribution.

Table 1: Demographics of the study groups

Variables	Group IR+ (n=30) Median (min-max)	Group IR- (n=20) Median (min-max)	*P*-value
Age (years)	66 (42-82)	63,5 (37-85)	0.165
Height (cm)	169 (156-185)	168 (150-176)	0.105
Weight (kg)	75 (63-95)	75 (59-85)	0.371
BMI (kg/m^2)	26.6 (20.8-31.7)	26.9 (20.7-35.6)	0.751
HOMA-IR	5.8 (2.5-23.6)	2.1 (1.1-2.4)f	<0.001

BMI: Body Mass Index, IR(+) with Insulin Resistance, IR(-) without Insulin Resistance, HOMA-IR: The Homeostatic Model Assessment of Insulin Resistance

Clinical and metabolic features

Analysis of the results showed that MDS-UPDRS scores were statistically significantly different between IR (+) and IR (-) groups ($P=0.034$). However, Modified Hoehn - Yahr ($P=0.300$) and FSS ($P=0.147$) scores were not statistically significantly different between the groups (Table 2).

Table 2: Clinical characteristics of the groups

Variables/Test	Group IR(+) (n=30) Median (min-max)	Group IR(-) (n=20) Median (min-max)	*P*-value
MDS-UPDRS	40 (18-59)	38 (12-73)	0.034
Modified Hoehn - Yahr	2.1 (1-5)	2.2 (1-5)	0.300
FSS	6 (1-7)	5.1 (1-7)	0.147

MDS-UPDRS: Movement Disorders Society-revised Unified PD Rating Scale, FSS: Fatigue Severity Scale, IR(+) with Insulin Resistance, IR(-) without Insulin Resistance

Discussion

In this study, we investigated association of insulin resistance on fatigue, the severity of the disease and motor disability in 50 patients with Idiopathic Parkinson's Disease. The results of this study showed that IPD patients with IR (+) (group 1) had higher motor disability which was assessed by MDS-UPDRS, than the IR (-) (group 2). Both group showed no significant difference in fatigue symptoms and disease severity.

The incidence of IR is 25% in healthy individuals, 60-75% in individuals with impaired glucose tolerance and 60-75% in patients with Type 2 diabetes [9]. In our study 30 patients (60%) insulin resistance was positive (IR+), the remaining 20 patients (40%) had negative insulin resistance (IR-).

Fatigue is a non-motor symptom of Parkinson's disease with a prevalence as high as 58% among affected patients [10]. More than 50% of patients with Parkinson's disease consider fatigue as one of the most disabling symptoms of PD but the causative mechanisms underlying fatigue have not been fully elucidated [11]. While peripheral mechanisms are partly involved in the pathophysiology of fatigue that occurs in CNS disorders, central abnormalities play a more significant role. Immune system dysregulation, impaired nerve conduction, neuroendocrine/neurotransmitter dysregulation, autonomic nervous system (ANS) involvement and energy depletion have all been implicated in the pathogenesis [12].

Proposed physiological mechanisms of fatigue associated with IPD include the role of circulating proinflammatory cytokines, impaired functioning of nigrostriatal and extrastriatal dopaminergic pathways and nondopaminergic (particularly serotonergic) pathways and involvement of the autonomic nervous system [13,14].

Based on this information, we investigated the relationship between fatigue in patients with IPD who did not have insulin resistance and had insulin resistance. In our current study, showed no significant difference in fatigue between IR (+) and IR (-) patients with IPD. However, this is the first study for literature which has specifically examined the relationship between fatigue and insulin resistance in IPD.

Recent studies have demonstrated that insulin has multiple functions in the brain and aberrant insulin signaling may have a role in the development of Alzheimer's disease and IPD. Insulin performs a variety of biological effects through its interaction with the insulin receptor, a transmembranous glycoprotein receptor tyrosine kinase. Downstream intracellular substrates of activated insulin receptor activate the PI3kinase/Akt pathway, thereby affect cellular functions. Additionally, mammalian target of rapamycin (mTOR) which is involved in the activation of PI3K/Akt via insulin induction is an important molecular junction of aging, diabetes and neurodegenerative diseases. It has been shown that the lifespan extension due to caloric limitation may be based on to suppression of mTOR, a cellular sensor of the nutrient environment of the organism. Although its interest to human lifespan remains unclear, the effect of caloric limitation-starvation on aging has been observed in a range of species from yeast to mammals [15]. Therefore, it is of great interest to determine whether therapeutically progressing

insulin resistance may affect disease severity and longevity in patients with IPD.

Bosso et al. [16] investigated that relationship between dementia and insulin resistance in patients with IPD. In this study, they showed that patients with dementia have higher prevalence of abnormal glucose metabolism, mainly IR, than nondemented patients. In other study, Schelp et al. [17] showed that there was a role of body composition, ageing and insulin resistance on amnestic dementia impairment in Parkinson's disease. Nakatsuji et al. [18] studied correlation of insulin resistance and motor function in spinal bulbar muscular atrophy (SBMA). In this study, they showed that insulin resistance is intensified in SBMA patients. Moreover, the degree of insulin resistance was strongly correlated with the severity of motor dysfunction in SBMA.

Although there were studies that showed the correlation of IR and motor disability in several neurodegenerative diseases, studies investigating the relationship between IPD patients and IR have not examined the relationship between disease severity and motor disability. In our study we investigated relationship with insulin resistance and motor disability. We found a significant difference in MDS-UPDRS scores between IR(+) and IR(-) patients. Increased insulin resistance has been associated with greater motor disability in IPD patients thoughtful of the idea of IR's effects on molecular pathways.

In literature, there were studies that investigating the relationship between IR and neurodegenerative disorders. Ruiz-Arguelles et al. [19] showed that insulin resistance in patients with Multiple Sclerosis is associated to the severity of the disease. But there was no significant difference on severity of disease between groups.

Fatigue is an important symptom that affects quality of life in patients with IPD, also characterization and assessment of fatigue would be helpful for proper diagnosis and management of fatigue. Therapeutic strategies for fatigue can only be developed after precise identification of its pathophysiology.

The limitation of this study is first the small number of patients. Also the effect of the drugs causing fatigue cannot be completely excluded in the neuropathy, cardiac and pulmonary system for reasons of association yet. Data obtained from the study examining the effect of insulin resistance on the development of fatigue indicated the need to elucidate the pathophysiology of fatigue as well as the need to demonstrate the association between fatigue and insulin resistance at the molecular level in IPD. Another limitation includes the lack of consideration of gender differences. Further studies can be planned by eliminating the effect of gender on insulin resistance. In addition, the effects of body mass index on insulin resistance should be considered in future studies.

In conclusion, in this study, a significant difference was found between insulin resistant and non-insulin resistant groups with respect to MDS-UPDRS scores. It has been recognized that increased insulin resistance results in greater motor disability through molecular mechanisms in patients with IPD.

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Impact of morphological measurements on symptoms in Chiari malformation type 1

Chiari tip 1 malformasyonunda morfolojik ölçümlerin semptomlar üzerine etkisi

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Abstract

Aim: Chiari malformation Type 1 (CM1) is a pathology resulting from herniation of cerebellar tonsils or tonsils into the spinal canal. We aimed to examine the impact of the cranium's morphological measurements on the symptoms with CM1 patients.

Methods: This research was designed as a retrospective case-control study in a single-center. 2309 patients aged between 18-70 who underwent brain magnetic resonance imaging (MRI) to confirm or exclude the diagnosis of CM1 as a result of clinical and examination findings were evaluated. Cranium's morphological measurements, the amount of herniation, patient's symptoms, and the modified Asgari score were retrospectively assessed.

Results: Patients with a final diagnosis of CM1 after the MRI evaluation were classified as study group (n=212), and the others control group (n=2097). The maximum cranial length, maximum cranial height, supra occiput length, posterior cranial fossa (PCF) anteroposterior length, in the study group were shorter, whereas the sagittal diameter of the foramen magnum and the longest anteroposterior diameter of the cerebrum were longer (P<0.001 for all mentioned comparisons). Tentorium cerebelli slope was found to be significantly lower in the study group (P<0.001). The most prevalent symptoms were a headache (92%). The herniation amount had a negative correlation with maximum cranial length and maximum cranial height (r=-0.184, P=0.07; r=-0.158 and P=0.022, respectively) and a positive correlation with the modified Asgari score (r=0.598; P<0.001).

Conclusion: The cranium's morphological measurements have an impact on the symptoms of patients with CM1.

Keywords: Chiari I malformation, Magnetic resonance imaging, Posterior cranial fossa, Tonsillar herniation

Öz

Amaç: Chiari Tip 1 malformasyonu (CM1) serebellar tonsil veya tonsillerin spinal kanala herniasyonu sonucu ortaya çıkan bir patolojidir. CM1 hastalarında kraniyumun morfolojik ölçümlerinin semptomlar üzerindeki etkisini incelemeyi amaçladık.

Yöntemler: Çalışmamız tek merkezde retrospektif vaka-kontrol çalışması olarak tasarlandı. Klinik ve muayene bulguları sonucunda CM1 olduğu düşünülen tanıyı kesinleştirmek veya dışlamak için beyin manyetik rezonans görüntüleme (MRG) yapılan, yaşları 18-70 arasında 2309 hasta değerlendirildi. Kranium, morfolojik ölçümleri, herniasyon miktarı, hastaların semptomları ve modifiye Asgari skoru retrospektif olarak incelendi.

Bulgular: MRG değerlendirilmesinden sonra kesin CM1 tanısı alanlar çalışma grubu (n=212) ve diğerleri kontrol grubu (n=2097) olarak hastalar sınıflandırıldı. Çalışma grubunda maksimum kranial uzunluk, maksimum kranial yükseklik, supraocciput uzunluğu, posterior kranial fossa (PCF) anteroposterior uzunluğu kısa iken, foramen magnumun sagital çapı ve serebrum'un en uzun ön arka çapı uzun idi. (hepsi için P<0,001). Çalışma grubunda tentorium serebelli eğimi belirgin olarak düşük saptandı (P<0,001). En sık görülen semptom baş ağrısıydı (%92). Herniasyon miktarı maksimum kranial uzunluk ve maksimum kranial yükseklik ile negatif korelasyon (sırası ile r=-0,184, P=0,07; r=-0,158, P=0,022) ve modifiye Asgari skoru ile pozitif korelasyon göstermekte idi (r=0,598; P<0,001).

Sonuç: Kraniyumun morfolojik ölçümleri CM1 hastalarının semptomlarını üzerinde etkilidir.

Anahtar kelimeler: Chiari I malformasyonu, Manyetik rezonans görüntüleme, Posterior kranial fossa, Tonsiller herniasyon

Introduction

Chiari malformation Type 1 (CM1) is a clinical condition that results from 5-mm herniation of one or 3–5 mm herniation of two cerebellar tonsils into the spinal canal [1-4]. Neurologic symptoms and findings may differ depending on herniation level and disruption of cerebrospinal fluid (CSF) circulation [5-7]. The etiology of the disease is unknown, although genetic factors, trauma, factors secondary to an infection, and deformations during the organogenesis period are suspected [5,8]. This pathology may occur alone or with other pathologies such as syringomyelia, scoliosis, odontoid retroflexion, basilar invagination, occipitalization of the atlas, and caudal migration of the brain stem. Symptoms may differ in the presence of these additional pathologies [5]. While the prevalence of the disease remains unclear, it has been reported to be 0.5% –0.9% [1,6,9,10]. Moreover, asymptomatic course of the disease in certain cases and mild symptoms observed in others hamper the clear determination of its prevalence [5].

CM1 is diagnosed with magnetic resonance imaging (MRI) following initial suspicion noted in the clinic. MRI evaluates posterior cranial fossa (PCF) along with the whole brain tissue and CSF flow, [1-4]. Neurologic symptoms and findings may differ depending on herniation level and disruption of CSF circulation [5-7]. The etiology of the disease is unknown, although genetic factors, trauma, factors secondary to an infection, and deformations during the organogenesis period are suspected [5,8]. This pathology may occur alone or with other pathologies such as syringomyelia, scoliosis, odontoid retroflexion, basilar invagination, occipitalization of the atlas, and caudal migration of the brain stem. Symptoms may differ in the presence of these additional pathologies [5]. While the prevalence of the disease remains unclear, it has been reported to be 0.5%–0.9% [1,6,9,10]. Moreover, asymptomatic course of the disease in certain cases and mild symptoms observed in others hamper the clear determination of its prevalence [5].

CM1 is diagnosed with MRI following initial suspicion noted in the clinic. MRI evaluates PCF along with the whole brain tissue and CSF flow, craniometric measurements. It enables the evaluation of angles, lines of intracranial structures, osteo-neural topographic images, cisterns, PCF pentagon, and localization of cerebellar tonsils [6].

Conservative treatment is recommended in mildly symptomatic or asymptomatic cases with less than 5 mm of tonsil ectopia, whereas surgical treatment is recommended in symptomatic cases [6].

The aim of the study was to analyze the impact of the cranium's morphological measurements in patients with CM1 on symptoms.

Materials and methods

Patient population and study design

Between January 1, 2015 and October 1, 2018, 2309 patients aged between 18-70 admitted to the neurosurgery clinic with various symptoms and referred to the radiology department for brain MRI with suspicion of CM1 after clinical and examination findings were evaluated retrospectively.

The local ethics committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study that was prepared according to ethical standards of 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000.

Exclusion criteria from the patients for the study were; having had a diagnosis of CMI, had a history of trauma, had brain surgery before, having increased intracranial pressure for some reasons, had a history of congenital craniocervical junction malformations and having pathological findings on the cranium structure.

Patients with a final diagnosis of CM1 after the MRI evaluation were classified as the study group (n=212), whereas the other patients were classified as the control group (n=2097). Age, sex, cranium, cerebrum and cerebellum morphological measurements, amount of herniation, the study group symptoms, and the modified Asgari score were evaluated.

MRI protocol and measurements

MRI was performed using two 1.5T MRI imaging scanners (Magnetom, Aera, Siemens, Erlangen, Germany) and Philips Achieva (Philips Medical Systems, Eindhoven, The Netherlands) with a standard head coil. The imaging protocol constituted the following five routine sequences: axial T1-weighted [repetition time (TR)/echo time (TE): 348/8.9 ms, voxel size: 0.7x0.7x0.5 mm, field of view (FOV): 23x23 cm, slice thickness: 5 mm]; axial T2-weighted (TR/TE: 4160/102 ms, voxel size: 0.6x0.6x5.0 mm, FOV: 23x23 cm, slice thickness:5 mm); axial FLAIR (TR/TE: 8000/86 ms, voxel size: 0.7x0.7x5.0 mm, FOV:23x23 cm, slice thickness: 5 mm); coronal T2-weighted (TR/TE: 4730/94 ms, voxel size:0.6x0.6x5.0 mm, FOV: 22x22 cm, slice thickness: 5 mm), and sagittal FLAIR (TR/TE: 9000/87 ms, voxel size: 0.4x0.4x5.0 mm, FOV: 23x23 cm, slice thickness: 5 mm).

The study group and the control group measurements were evaluated on MRI via Extreme Picture Archiving and Communications System (PACS) system (Ankara, Turkey).

Patients whose cerebellar tonsil(s) into the spinal canal 3 mm beyond the basion-opisthion line was accepted as the study group.

We used Houston et al. criteria to determine the mid-sagittal plane in the MRI sections, at least three of the following four structures should be seen in a single sagittal view; the genu of the corpus callosum, the splenium of the corpus callosum, the pituitary infundibulum and the cerebral aqueduct. Measurements were taken on the mid-sagittal FLAIR images. The standard measurement methods stated in the literature were used [11-14]. Length measurements in millimeters and angle measurement were made in degrees.

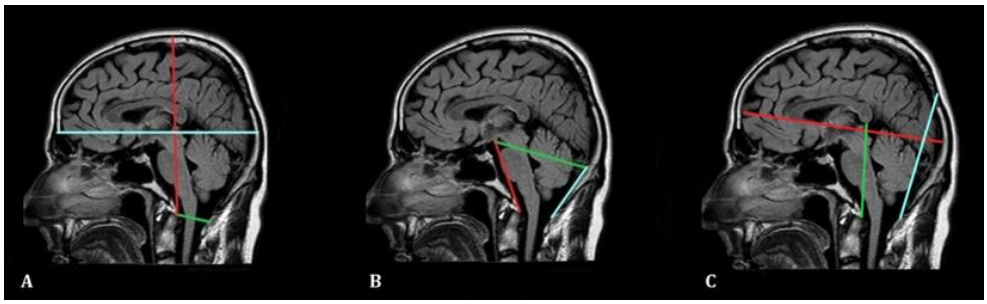

Figure 1: Sagittal FLAIR (A, B, C), an image demonstrating the distance measurements. (A) Maximum cranial length is shown by a blue line, maximum cranial height is depicted by a red line, foramen magnum sagittal diameter is shown by a green line. (B) Supra occiput length shown by a blue line, clivus length is depicted by a red line, posterior cranial fossa anteroposterior length is shown by a green line. (C) The occipital cord length is shown by a blue line, longest anteroposterior diameter of the cerebrum depicted by a red line, posterior height of the cranial fossa is shown by a green line.

Maximum cranial length (C1): is the line between glabella-opisthocranion, Maximum cranial height (C2): is the line between basion-vertex, Foramen magnum sagittal diameter (C3): is the line between basion-opisthion (Figure 1A), Supra occiput length (C4): is the line between opisthion-protuberentia occipitalis interna, Clivus length (C5): is the line between basion-dorsum sellae top edge, PCF anteroposterior length (C6): is the line between dorsum sellae-protuberentia occipitalis interna (Figure 1B), Occipital cord length (C7): is the line between opisthion-lambda, Longest anteroposterior diameter of the cerebrum(C8): is the line between polus frontalis-polus occipitalis, Posterior height of the cranial fossa (C9): is the perpendicular line between inferior of the corpus callosum splenium to foramen magnum plane (Figure 1C).

Tentorium cerebelli slope (A): is the angle between the cerebellum tentorium and the supra occiput length (Figure 2).

Tonsillar herniation (TH): is the distance between the tip of the cerebellar tonsils and opisthion - basion line (Figure 3) [14].

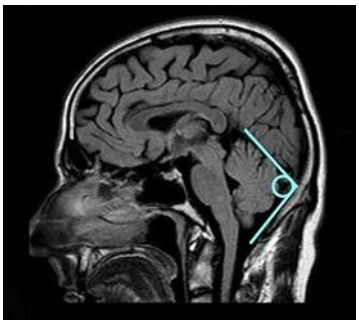

Figure 2: Sagittal FLAIR image demonstrating the tentorium cerebelli slope is shown as the angle between the blue lines

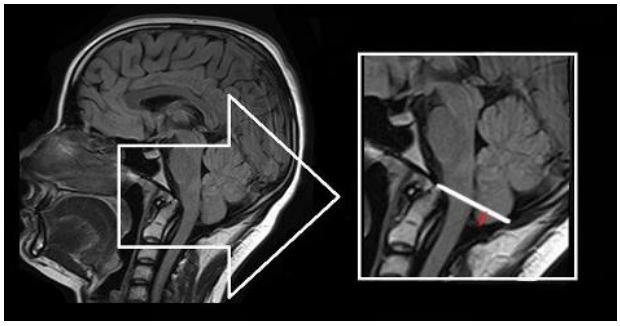

Figure 3: Sagittal FLAIR image demonstrating basion-opisthion line in white and tonsillar herniation measurement as a red line

All measurements were performed by the same observer. To test the intra-observer reliability, the same radiologist repeated all measurements three months after the first assessment. To test the inter-observer reliability, another radiologist blinded performed quantitative and semi-quantitative measurements of randomly selected patients and control groups 1000 brains among 2309 brains.

Symptoms of the study group were evaluated. The modified Asgari score, which is determined prior to surgeries, was used to evaluate the severity of the lesions. The relationship among the modified Asgari score, measurements, and age were evaluated.

Statistical analysis

The SPSS package (Statistical Package for the Social Sciences for Windows, Version 22.0, SPSS Inc., Chicago, IL, U.S.A.) was used for data analysis in our study. Kolmogorov–Smirnov test was used for evaluating the distribution of variables, whereas Pearson's Chi-Square test was used for the analysis of qualitative data. Spearman's correlation test was used in the analysis of quantitative data, whereas the student's t-test was used in the comparison of qualitative data and quantitative data. $P<0.05$ was accepted as the level of statistical significance. The intra- and interobserver reliability of MRI examinations were tested using Kappa statistics.

Results

CM1 was detected in 212 (9.2%) out of 2309 patients included in the study. The mean age of the patients was 39.3 (13) years and there was no difference between the study and the control groups in terms of age ($P=0.543$). Of the patients, 53.3% were male, and the number of males in the study group was significantly higher ($P=0.007$). While the C1, C2, C4, C5, C6, and C7 lengths were significantly shorter in the study group, it was found that the C3 length was significantly longer ($p < 0.001$ for all mentioned comparisons). C8 and C9 lengths were significantly shorter in the study group ($P<0.001$). The slope of tentorium cerebelli was found to be significantly smaller in the study group ($P<0.001$). Herniation length of the study group was determined as 8 (1.6) mm, and the modified Asgari score was determined as 4.8 (1.9) (Table 1).

The most prevalent symptoms were a headache (92%) and neck ache (35.4%) (Figure 4).

In the study group, it was observed that age had a positive correlation with C1, C3, C6 (r=0.515, $P<0.001$; r=0.467, $P<0.001$; r=0.572, $P<0.001$, respectively) and a negative correlation with C4, C8, C9, and tentorium cerebelli slope (r=-0.390, $P<0.001$; r=-0.212, $P=0.002$; r=-0.446, $P<0.001$, respectively) (Table 2). The herniation amount had a negative correlation with C1 and C2 (r=-0.184, $P=0.07$; r=-0.158, $P=0.022$, respectively) and a positive correlation with the modified Asgari score (r=0.598, $P<0.001$) (Table 2).

Intra and interobserver intraclass correlation coefficients for all quantitative and semi-quantitative measurements were 0.81 and 0.87, respectively.

Table 1: Comparison of cranium, cerebrum and cerebellum morphological measurements of study group and control groups

		Study group (n=212)	Control group (n=2097)	*P*-value
Age mean (SD)		39.3 (13)	38.7 (12)	0.543*
Sex. n (%)	Male	113 (53.3)	915 (43.6)	0.007**
	Female	99 (46.7)	1182 (56.4)	
		mean (SD)	mean (SD)	
C1		171.4 (2.7)	174.3 (1.7)	<0.001*
C2		129.6 (1.9)	134.5 (1.6)	<0.001*
C3		35.6 (2.3)	33.9 (2.3)	<0.001*
C4		42.6 (2.3)	44.9 (17.7)	<0.001*
C5		39.2 (1.9)	42.3 (2.1)	<0.001*
C6		76.8 (2.5)	77.8 (3.6)	<0.001*
C7		90.7 (1.9)	92.6 (4)	<0.001*
C8		151 (2.4)	151.7 (2.4)	<0.001*
C9		56.9 (2.2)	59.2 (2.3)	<0.001*
A		88.4 (1.9)	89.6 (1.8)	<0.001*
TH		8 (1.6)		
Modified Asgari score		4.8 (1.9)		

SD: Standard deviation, C1: Maximum cranial length, C2: Maximum cranial height, C3: Foramen magnum sagittal diameter, C4: Supra occiput length, C5: Clivus length, C6: Posterior cranial fossa anteroposterior length, C7: Occipital cord length, C8: Longest anteroposterior diameter of the cerebrum, C9: Posterior height of the cranial, A: Tentorium cerebelli slope, TH: Tonsillar herniation length, * Student's t-test, ** Chi-Square test

Table 2: Comparison of cranium, cerebrum and cerebellum morphological measurements with study group's age, herniation, and the modified Asgari score (Spearman's correlation test)

	Age		TH		MAS	
	r	*P*-value	r	*P*-value	r	*P*-value
C1	0.515	<0.001	-0.184	0.007	-0.104	0.130
C2	0.039	0.574	-0.158	0.022	-0.141	0.040
C3	0.467	<0.001	-0.020	0.767	0.026	0.705
C4	-0.390	<0.001	-0.037	0.588	-0.040	0.558
C5	-0.131	0.057	-0.110	0.110	-0.089	0.197
C6	0.572	<0.001	-0.027	0.699	0.038	0.584
C7	-0.064	0.354	0.100	0.148	-0.004	0.956
C8	-0.212	0.002	0.078	0.255	-0.021	0.758
C9	-0.446	<0.001	0.006	0.936	-0.085	0.218
A	-0.178	0.009	0.129	0.061	0.120	0.081
TH	-0.127	0.065		1.000	0.598	<0.001
MAS	-0.122	0.077	0.598	<0.001		1.000

C1: Maximum cranial length, C2: Maximum cranial height, C3: Foramen magnum sagittal diameter, C4: Supra occiput length, C5: Clivus length, C6: Posterior cranial fossa anteroposterior length, C7: Occipital cord length, C8: Longest anteroposterior diameter of the cerebrum, C9: Posterior height of the cranial, A: Tentorium cerebelli slope, TH: Tonsillar herniation length, MAS: Modified Asgari score

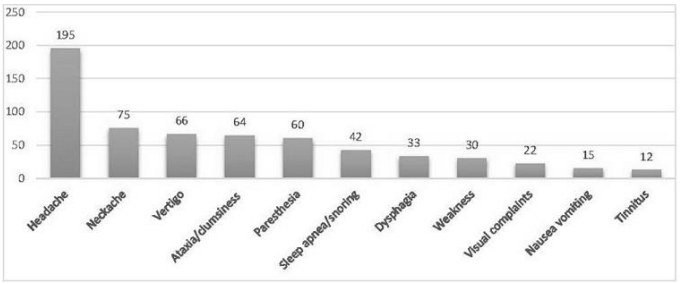

Figure 4: Symptoms in the study group

Discussion

Although genetic defects and defects during the embryologic period are considered to cause CM1, it has been reported that CM1 can develop during the period after birth and that the existing disease can progress or regress over time. Moreover, etiology of CM1 includes gene mutations occurring during the embryologic period, teratogenicity, and abnormal mechanical force(s) which can result in shape defects in the skull [6]. To prevent the progression of CM1, surgical treatment is recommended as soon as possible for patients with CM1 exhibiting progressive or persistent symptoms and/or widening syringomyelia. Moreover, it has been reported that the symptoms may regress after the application of this treatment [8].

The prevalence of CH1 was reported as 0.5%–0.9% in various populations [1,6,9,10]. In our study, we found the prevalence as 9.2% on brain MRI, much higher compared to other studies in the literature. The patients in our study group were suspected of CM1 after clinical and examination findings.

In studies conducted on adult patients, the mean age has been reported to be between 36 and 43 years [14-16]. The mean age of the study group in our study was 39.3 (13) years, which is similar to that reported in the literature. We believe that CM1 is prevalently detected in young adult patients as a result of MRI scans performed to identify the etiology of symptoms such as long-term headaches.

Various studies describe that CM1 has a higher prevalence among women than among men [6,14,16]. Arnautovic et al. [15] reported that CM1 is more prevalent among women, and suggested that the cause for this is the coincidental identification of lesions in women while determining the cause of headaches. In contrast with the literature, the prevalence was higher among male patients in our study group, and this may be related to the differences between societies and the number of male patients admitted.

It is considered that the defect in the cranial structures in CM1 occurs during the intrauterine period as a result of the disruption of the spinal migration [9]. It has been stated that patients with CM1 have larger foramen magnum and smaller PCF than control patients [9,17]. Houston et al. observed that fastigium height, pons height, corpus callosum height, clivus length, and PCF height are shorter in patients with CM1, McRae line length are higher whereas the PCF volume is similar to those in the control group [11]. In the same study, it was emphasized that the condition leading to CM1 was due to abnormalities at many points of the cranium [11].

In their study, Taştemur et al. [14] stated that in individuals with tonsillar herniation, foramen magnum sagittal diameter, cerebellum height, and cerebellum sagittal diameter increases, whereas the maximum cranial height, supraocciput length, clivus length, and fossa cranii posterior height decreases. It has been stated that the cranium would bend forward and the tonsils would be lower in the case of short villus and hypoplastic condyle [6]. It was found in our study that the bone structures of the study group were smaller and foramen magnum was larger. Microcephaly or early closing of sutures for any reason (such as genetic factors, trauma, and injective agents) during organogenesis and following periods may have caused the head to be smaller. This condition may have led to the movement of the parenchymal tissues toward the space/gap (spinal canal) into which they could move. Moreover, this herniation may have caused the widening of the foramen magnum. Houston et al. reported that the structures within PCF are lower in patients with CM1 than the control group [11]. Taştemur et al. [14] stated that the cerebellar structures in patients with CM1 were larger than in those in the control group in their study. Poretti et al. [6] reported that herniation occurs when there is excess parenchymal tissue within PCF. In our study, it was observed in the control group that the cerebral tissue in the parenchyma was larger, it grew in the vertical axis, and it was narrower in other axes. We believe that parenchymal tissue did not fit inside the cranium owing to its excessive amount, and the overflowing area pressured the cerebellar tissue and caused herniation of the cerebellar tissue into the spinal canal. Parenchymal tissues may thus have the tendency to grow in the vertical plane.

Houston et al. [11] and Taştemur et al. [14] stated that although the slope of the tentorium cerebelli is smaller in the

CM1 group than the control group, there is no significant difference. In our study, the tentorium cerebelli slope was found to be significantly lower in the study group. We believe that the cerebellar tissue was pushed forward owing to the narrowness of the angle. The cerebellum was thus longer in the vertical axis, and the cerebellum that was unable to fit into the PCF shifted toward the spinal canal.

Approximately 37% of pediatric patients with CM1 are asymptomatic and such patients are diagnosed by coincidence [6]. Yarbrough et al. [18] stated that the clinical findings and symptoms of patients with CM1 may vary, and the results of these findings/symptoms can also differ among patients. It has been suggested that the pressure caused by the soft tissue and bone structures on PCF and spinal canal result in the development of symptoms [9]. It has been reported that the most prevalent symptoms in CM1 are a headache, neck ache, poor balance, and cognitive function disorder [6,8,19]. Gilmer et al. stated that the most commonly encountered symptoms among the patients in their study were a headache (93.1%) and neck ache (47.9%) [20]. Lei et al. [16] reported that the most prevalent symptoms among patients are headache and neck ache (73%), sensory disorder (58.9%), and motor weakness (41%). In our study, the most prevalent symptoms were determined as a headache and neck ache which is consistent with the literature. We believe that headache and neck ache is the most prevalent indications of increased intracranial pressure secondary to the disrupted CSF circulation.

In addition, we believe that the other symptoms emerge in parallel to the rate at which the centers in the herniated area are affected.

CM1 herniation can be as small as 3 mm and as large as 25 mm [11]. Taştemur et al. [14] reported the average herniation amount in individuals with tonsillar herniation of 4.85 (3.09) mm. Lei et al. [16] reported the amount of tonsil ectopia in patients to be 13.6 mm. CM1 causes the increase in the amount of tissue within foramen magnum and this disrupts the CSF circulation. As the amount of tissue increases, CSF circulation becomes more disrupted and in parallel with this, the patient's symptoms worsen [18]. Moreover, there are studies stating that there is no relationship between the level of herniation and the severity of symptoms [10,20]. In our study, it was detected that the amount of herniation was 8 (1.6) mm, and it had a positive correlation with the modified Asgari score. We believe that the increase in the amount of herniation would cause further disruption in CSF pressure and/or result in an increase in the areas being subjected to pressure, making the symptoms become even worse.

Gilmer et al. [20] stated in their study that the symptoms of patients in advanced ages are less and that there is a negative correlation between Chicago Chiari Outcome Scale and age. In this study, it was stated that although CM1 is a congenital abnormality, the patients can become symptomatic at any age and the symptoms can change over time. In the anamneses obtained from symptomatic geriatric patients, it was noted that CM1 actually existed congenitally or since childhood and became worse [20]. In our study, it was found that in parallel with the increase in age, bone structures grew with the decrease in parenchyma tissues. However, there was no relationship noted between age and clinic. We believe that bones continue to grow with age and the formed bone structure is osteoporotic; moreover, there is a decrease in the parenchyma tissue simultaneously owing to atrophy. We believe that the space within the cranial cavity increases with age but the herniated tissue does not go back to its previous location, and the symptoms do not change due to the permanence in the bone changes related to CM1 (such as the widening of the foramen magnum, and clivus shortness).

Previous studies show that the narrowness of PCF or the excess in parenchyma plays a role in herniation [6,11,14]. An earlier study stated that a 2-mm change in the intracranial distance can cause considerable differences in the patient's symptoms [11]. In our study, it was found that the amount of herniation and the modified Asgari score had a negative correlation with the size of cerebral structures and a positive correlation with the length of the cerebellar structure. We believe that the amount of herniated tissue increases largely owing to the decreased volume in the PCF and the excessive parenchymal tissue. Longer cerebral structures may be an indicator of an increased amount of herniation. Thus, the patient's symptoms may have been worsened in relation to the amount of herniation. Its negative relationship with the cranial length may have resulted in a possible excess of parenchyma, causing the parenchyma tissue to shift not into the spinal canal but into the cranium.

Our study has certain limitations. Our study had a retrospective design, and it was based on the patient file analyses. Further studies showing the correlation of CM1 symptoms with radiological measurements are needed.

Conclusion

The bone structures forming the cranium have an effect on the symptoms of patients with CM1. It was particularly determined that the pathologies causing the narrowing of the volume of the posterior fossa were related to tonsillar herniation.

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Assessment of axillary hyperhidrosis and bromhidrosis treatment with microwave technology

Mikrodalga teknolojisi ile aksiller hiperhidroz ve bromhidroz tedavisinin değerlendirilmesi

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Abstract

Aim: Hyperhidrosis and bromhidrosis are disorders related with generalized or local excessive sweating that can have a significant impact on the quality of life of patients who suffer from them. There are several treatments, both topical and invasive, with permanent or temporary effects. In recent years, microwave technology has emerged as a non-invasive procedure with permanent effects and few side effects. The study aim was to evaluate the efficacy, safety and satisfaction degree of patients with axillary hyperhidrosis and bromhidrosis treatment using microwave technology, and the primary outcome was to increase patient satisfaction about their sweating levels.

Methods: Retrospective cohort study is planned and included the patients underwent a single microwave session with miraWave® technology for hyperhidrosis or bromhidrosis. Efficacy and safety were assessed at one, three, six, and 12 months. Inclusion criteria were men or women between 18-65 years old, diagnosed with hyperhidrosis and an HDSS score of 2-4. Patients with pacemakers and expectant or lactating mothers were excluded. Before treatment, patients were diagnosed using the Hyperhidrosis Disease Severity Scale, and the Minor test. Satisfaction was assessed through a subjective assessment of the satisfaction level, using a questionnaire in which participants chose the sentence that best fitted with an assigned score of 0-10.

Results: A total of 46 patients participated in the study: 20 women (43.48%) and 26 men (56.52%) aged between 18-65 years old. Throughout the follow-up period, an average of 49.88% of patients reported a subjective improvement of hyperhidrosis and 95% reported the same about bromhidrosis. After comparing the results of their previous level of sweating with those after one year of treatment, 80.40% of patients showed themselves satisfied. All side effects were resolved in a time not exceeding 10 weeks.

Conclusion: Microwave technology proves to be an effective and lasting treatment after one single session for axillary hyperhidrosis and/or bromhidrosis.

Keywords: Axillary hyperhidrosis, Axillary bromhidrosis, Microwave technology, Axillary glands

Öz

Amaç: Hiperhidroz ve bromhidroz, bunlardan muzdarip olan hastaların yaşam kalitesini önemli ölçüde etkileyebilecek genelleştirilmiş veya lokal aşırı terleme ile ilgili bozukluklardır. Kalıcı veya geçici etkileri olan hem topikal hem de invaziv olan birkaç tedavi vardır. Son yıllarda, mikrodalga teknolojisi kalıcı etkiler ve az yan etki ile non-invaziv bir prosedür olarak ortaya çıkmıştır. Çalışma amacı, aksiller hiperhidroz ve bromhidroz tedavisi alan hastaların mikrodalga teknolojisi kullanılarak etkinlik, güvenlik ve memnuniyet derecelerini değerlendirmek ve birincil sonuç, terleme düzeyleriyle ilgili hasta memnuniyetini araştırmaktır.

Yöntemler: Retrospektif bir kohort çalışması planlandı ve hiperhidroz veya bromhidroz için miraWave® teknolojisi ile tek bir mikrodalga seansı geçiren hastalar dahil edildi. Etkinlik ve güvenlik bir, üç, altı ve 12 ayda değerlendirildi. Dahil edilme kriterleri, 18-65 yaşları arasında, hiperhidroz ve HDSS skoru 2-4 olan kadın veya erkeklerdir. Kalp pili ve hamile veya emziren anneleri olan hastalar çalışma dışı bırakıldı. Tedaviden önce hastalara Hiperhidroz Hastalığı Şiddet Ölçeği ve Minor testi ile tanı kondu. Memnuniyet, memnuniyet seviyesinin öznel bir değerlendirmesi ile değerlendirildi, katılımcıların en iyi 0-10 puan almış bir cümleyi seçtikleri bir anket kullanıldı.

Bulgular: Çalışmaya toplam 46 hasta katıldı: 20 kadın (%43.48) ve 18-65 yaşları arasındaki 26 erkek (%56.52). Takip süresi boyunca, hastaların ortalama %49.88'i hiperhidrozun subjektif bir iyileşmesini ve %95'i bromhidroz konusunda aynı olduğunu bildirdi. Önceki terleme seviyelerinin sonuçlarını bir yıllık tedavi sonrası durumla karşılaştırdıktan sonra, hastaların %80.40'ı kendilerinin tatmin olduğunu ifade etti. Tüm yan etkiler 10 haftayı geçmeyen bir sürede yok oldu.

Sonuç: Mikrodalga teknolojisi, aksiller hiperhidroz ve / veya bromhidroz için tek seanstan sonra etkili ve kalıcı bir tedavidir.

Anahtar kelimeler: Aksiller hiperhidroz, Aksiller bromhidroz, Mikrodalga teknolojisi, Aksiller bezler

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Introduction

Hyperhidrosis is a condition characterized by generalized or local excessive sweating. Primary hyperhidrosis is usually local and affects one or more areas of the body, generally in a symmetrical manner, especially the palms of the hands, the armpits, the soles of the feet, or the face [1]. Its origin is idiopathic, although it has been suggested that it may be the result of hyperactivity of the sympathetic system. It has an incidence of about 3% and usually appears between 25-64 years old [2]. Secondary hyperhidrosis is usually generalized, affecting the entire body, and its origin is an underlying cause, like an infectious, endocrine or neurological disorder [3].

On the other hand, bromhidrosis is characterized by body odor and is closely related with excessive sweating. Corynebacterium is believed to be significantly involved in the biotransformation of natural, odorless secretions in volatile, smelly molecules in the armpit [4].

These disorders may have a significant impact on the quality of life and professional, social and emotional burden of the people suffering from them [5]. This situation has prompted efficacy studies to be conducted with new treatments with minimum side effects. The options to treat hyperhidrosis include topical treatment with aluminum chloride and oral anticholinergic drugs, which in most mild-to-moderate cases are enough. Injections of botulinum toxin A [6], sympathectomy and local excision are also highly effective [7], but they are reserved for cases that are resistant to conservative therapy, although there still could be side effects, like compensatory sweating after an endoscopic transthoracic sympathectomy [8].

For some years, microwave-based technology has been added to these treatments [9], with good results reported in studies conducted for the treatment of underarm sweating [10-12]. It is a local, non-invasive procedure that uses non-ionizing energy with a frequency of 5.8 MHz. Its design enables it to deliver energy with precision at the depth of sweat glands (located 2-5 mm deep) [8], and produce thermolysis of the eccrine and apocrine glands, eliminating them permanently and, consequently, reducing sweat volume and bad odor.

Possible post-treatment side effects are edema and/or pain with some degree of intensity for three days after treatment, inflammation and occurrence of nodules in the armpit 7-15 days after treatment, hematomas in the anesthesia puncture site, redness due to the suction procedure, or permanent loss of underarm hair since it also acts on hair follicles [8], resolving after a few weeks. Compensatory sweating rarely occurs since axillary sweat glands make up 3% of the entire body and, with this technique, only about 66.6% of axillary sweat glands are eliminated.

The objective of this study was to use patients' subjective post-treatment assessments during a follow-up period of one year to evaluate the efficacy of axillary hyperhidrosis and bromhidrosis treatment using microwave technology.

Materials and methods

Study design

This was an observational, retrospective, cohort study, single-center, open study conducted at the Clínica Tufet (Barcelona, Spain). It included men and women between 18 and 65 years old, diagnosed with axillary hyperhidrosis and/or bromhidrosis based on the Hyperhidrosis Disease Severity Scale (HDSS).

The study was conducted in compliance with the principles laid down in the current revised version of the Declaration of Helsinki, Good Clinical Practices (GCPs), and all the relevant applicable laws and regulatory requirements for the use of medical devices in Spain. Individual material logs were kept in the investigator's source documents, and case report forms did not include any personal information.

Inclusion criteria: Men or women between 18-65 years old, diagnosed with hyperhidrosis and an HDSS score of 2-4.

Exclusion criteria: Patients with pacemakers, and expectant or lactating mothers.

The primary outcome was to increase patient satisfaction about their sweating levels.

Study protocol

After accepting to participate in the study, and if they met all inclusion criteria, patients were subjected to one single microwave session with the miraDry® device (Miramar Labs, Santa Clara, CA), which uses miraWave® technology.

The system is designed to be used by medical professionals in a properly prepared site. It applies precise amounts of microwaves on the soft tissue of the armpit with a frequency of 5.8 GHz to treat excessive sweating in a superficial, local and non-invasive way. While microwaves are applied, the device protects the surface of the tissue by means of an active contact cooling system. It has a console with a main body and a touch screen, a bioTip and a handpiece.

Pre-Treatment procedures

HDSS scale adapted to Spanish: Patients will use this scale to classify their hyperhidrosis by choosing one of the following statements:

- Score 1: My sweating is never noticeable and never interferes with my daily activities.
- Score 2: My sweating is tolerable but sometimes interferes with my daily activities.
- Score 3: My sweating is barely tolerable and frequently interferes with my daily activities.
- Score 4: My sweating is intolerable and always interferes with my daily activities.

A score of 3-4 is for severe hyperhidrosis, a score of 2 is for moderate hyperhidrosis, and a score of 1 is for absence of hyperhidrosis.

Minor test: Most commonly used in clinical practice, it is based on the color that the skin assumes when the sweat of the study area touches certain chemical substances (iodine solution followed by corn starch). The solution turns blueish in those areas with more sweating, enabling to locate those areas of maximum perspiration, as well as to assess the result after treatment.

Subjective assessment of the satisfaction level: It is performed by choosing the best fitted sentence, which has an assigned score of 0-10:

- 0: I am not happy; the treatment did not work.
- 1-4: I am not very happy, the treatment barely worked.
- 4-6: I am moderately happy, the treatment moderately worked.
- 6-8: I am happy, the treatment worked.
- 9-10: I am very happy; the treatment has met all my expectations.

Treatment protocol

It was a local, non-invasive, long-acting procedure, not indicated for the treatment of hyperhidrosis in other areas of the body. First, the patient's armpit was measured to determine the grid pattern to be used, which conditioned the number and place of impact points. Then, tumescent anesthesia (Klein solution) was applied through four entry points. This type of anesthesia enabled to work with more efficacy and safety, and with less amount of anesthetic than necessary when the point-by-point technique was used. Volume ranges from 70-130 ml of solution per armpit, depending on its size.

Once the area was anesthetized, the handpiece was applied on those points predetermined by the grid pattern. The device had different types of intensity (1-5), being the maximum level (Level 5), the more successful, and the lowest was reserved for the upper area of the armpit to avoid accidentally damaging the brachial plexus. Based on the amount of subcutaneous fat, sensitivity, and the desired result, energy levels determine the volume and depth of the treatment, at the same time preserving most of the dermis. The handpiece acted over an area of 10 x 30 mm, so, depending on axillary size, the treatment was required between 30-45 minutes per armpit.

As a safety measure and to increase efficacy and protect the dermis, the device had a skin suction and cooling system. During the treatment cycle, cooling fluid flowed through a chamber in contact with the skin, protecting the epidermis and upper dermis from excess heating - this procedure allowed to protect structures that are deeper than sweat glands from heat injury. Furthermore, the frequency and structure of the antennae can be adapted to limit penetration, focusing the irradiated microwave energy on the dermal/hypodermal interface.

The energy was delivered for about 30 seconds, followed by a 20-second post-cooling period. Upon completion, the vacuum was released, and the cessation of the audio signal indicated the end of the treatment cycle. The operator then moved the handpiece to the next adjacent treatment area, and the process was repeated.

Post-Treatment

After treatment, patients were prescribed anti-inflammatory drugs, like dexamethasone or ibuprofen and local cold packs. They were also recommended to use antiseptic soap to wash the area, avoid going to pools, spa resorts, saunas or the beach, and do not exercise four days after treatment.

Patient follow-up

Treatment efficacy and safety was assessed 1, 3, 6 and 12 months after treatment. Post-treatment follow-up visits included patient subjective assessments of treatment efficacy; all adverse effects were recorded. At the end of 12 months, all patients were provided a satisfaction questionnaire.

Data assessment

Variables analyzed were gender, age, family history of hyperhidrosis, prior treatments, type of hyperhidrosis, patient subjective assessment of their treatment result, global satisfaction, secondary effects and duration of the treatment.

Statistical analysis

Unless otherwise noted, quantitative variables are described as mean and standard deviation (SD), whereas categorical variables are expressed as percentages.

Results

A total of 46 patients participated in the study: 20 women (43.48%) and 26 men (56.52%) aged between 18-65 years old.

Pre-Treatment evaluations

Forty-two (91.32%) patients were initially diagnosed with primary hyperhidrosis, of which 17 (40.47%) had concomitant bromhidrosis. One (2.17%) patient was diagnosed with secondary hyperhidrosis due to a surgery. Three (6.51%) were diagnosed with bromhidrosis without hyperhidrosis. Twelve (26.09%) patients had family history of hyperhidrosis.

Regarding patients' prior treatments, the percentages were as follows: 16 (34.78%) were treated with topical antitranspirants, five (10.87%) with Botox injections, one (2.17%) with laser, one (2.17%) with sympathectomy, one (2.17%) with oral anticholinergics, and 22 (47.82%) had no prior treatments.

Evaluations after 12 months

Mean patient subjective assessments of treatment results using the scores obtained in follow-up visits were as follows:

- Of patients treated for hyperhidrosis, 20.93% (n=9) assessed the treatment result between 1-4 (“I am not very happy, the treatment barely worked”); 51.16% (n=22) between 4-6 (“I am moderately happy, the treatment moderately worked”); and 27.9% (n=12) between 6-8 (“I am happy, the treatment worked” (Figures 1 and 2). Therefore, 34 (79.06%) patients noticed a subjective improvement after treatment. The mean value of the subjective assessment was 4.99 (0.81) over 10.
- Regarding patients treated for bromhidrosis, 9.09% (n=2) assessed the treatment result between 6-8 (“I am happy, the treatment worked”), and 90.9% (n=20) between 9-10 (“I am very happy, the treatment has met all my expectations”) (Figures 3 and 4). Therefore, 22 (100%) patients noticed a subjective improvement after treatment. The mean value of the subjective assessment was 9.5 ±0.58 over 10.
- Mean response for both treatments was 89.53%.

Based on the satisfaction survey conducted at the end of the follow-up period (12 months), 79% of patients showed themselves very satisfied, 15% were satisfied, 6% were not too satisfied and no patients were unsatisfied (Figure 5).

Safety data

Regarding reported adverse effects, 100% (n=46) of patients showed edema, 95.65% (n=44) had hematoma in the anesthesia puncture sites, 69.56% (n=32) had subcutaneous nodules, 65.21% (n=30) had local alteration of sensitivity, and 2.17% (n=1) had axillary fibrous tissue. Side effects were resolved in an average of 1-10 weeks, depending on their severity (Table 1).

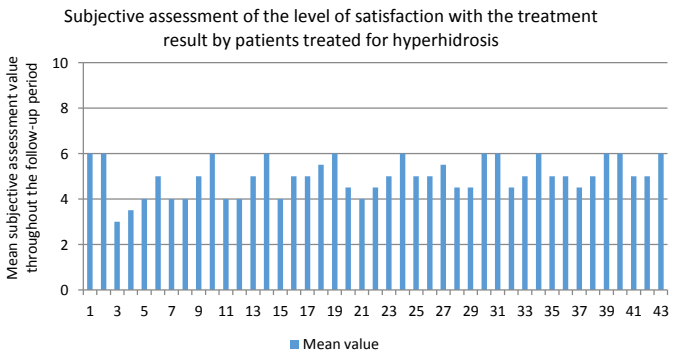

Figure 1: Mean subjective assessment of the level of satisfaction with the treatment result by patients treated for hyperhidrosis throughout the follow-up period (1, 3, 6 and 12 months)

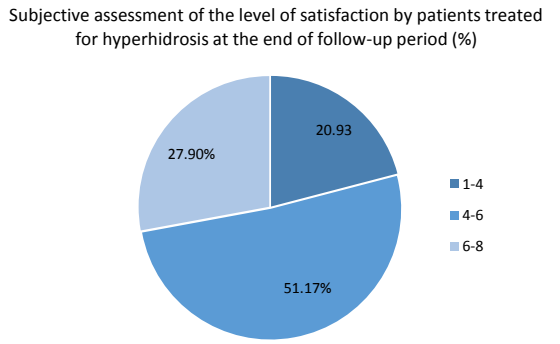

Figure 2: Subjective assessment by patients treated for hyperhidrosis upon completion of the follow-up period

Figure 3: Mean subjective assessment of the level of satisfaction with the treatment result by patients treated for bromhidrosis throughout the follow-up period (1, 3, 6 y 12 months)

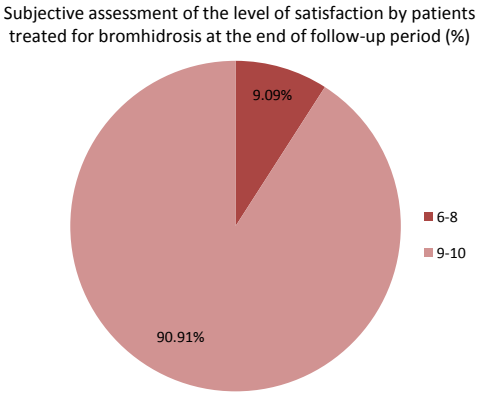

Figure 4: Subjective assessment by patients treated for bromhidrosis upon completion of the follow-up period

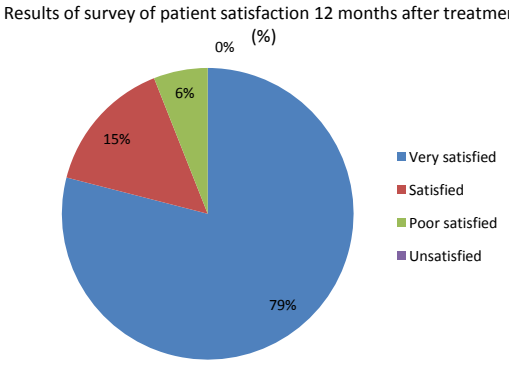

Figure 5: Result of patients' satisfaction survey conducted after 12 months of treatment

Table 1: Side effects and time of remission of symptoms

Side effects	Number of patients	%	Duration of symptoms (weeks)
Edema	46	100.00	1-1.4
Hematoma	44	95.65	1
Subcutaneous nodules	32	69.56	8-10
Local alteration of sensitivity	30	65.21	8-10
Axillary fibrous tissue	1	2.17	5
Eczema	0	0.00	-

Discussion

Microwave technology complies with the ideal requirements for the treatment of hyperhidrosis since it is focused, non-invasive, long acting and with minimum adverse effects. In our study, patients of both groups reported a mean response of 89.53%. Despite being a technology that has only been applied to the treatment of these disorders fairly recently, we already have results from randomized, long-term studies that ensure its efficacy and safety [10,11].

In the blind, randomized study by Glaser et al. [10], an active treatment group (n=81) was compared with a sham treatment group (n=39). The efficacy in the active treatment group, defined as a drop in HDSS to a 1 or 2 score after one year of follow-up, was of 74.75% (mean of all results obtained at follow-up visits). Likewise, the >50% reduction percentage, assessed with gravimetry, was 72.67% after 6 months. Adverse events were mild and resolved spontaneously.

In the first follow-up report from the long-term study by Lupin et al. [11], 26 patients showed 96.55% efficacy of treatment, defined as a drop in HDSS to a 1 or 2 score after 12 months, and 19 patients showed 98.19% efficacy after 24 months. This study also assessed patients' quality of life through the Dermatology Life Quality Index (DLQI), which was also used to evaluate the effect of the treatment as a higher or equal reduction to 5 score points. Results obtained had an average of 72.67% at 24 months. One year after treatment, all side effects (except underarm hair loss) had resolved. No patients showed new side effects during the second year. Differences concerning efficacy between both studies may be due to the difference in the number of patients.

In the study by Hong et al.[9], with 31 patients, of which 26 completed it, efficacy results between 74.3%-99.2% were obtained based on an HDSS score reduction to 1 or 2 after one year of follow-up, and a reduction percentage of DLQI that is higher or equal to 5 score points between 66.3%-99.9%. In this study, it was also observed that the treatment affected underarm odor. The percentage of patients that reported their body odor as not noticeable after 12 months of follow-up was 68.55%. Treatment efficacy didn't seem to vary with the number of procedures, and short-term adverse events related with therapy were usually minor. The most common were post-treatment edema, erythema and local discomfort, which resolved quickly after therapy.

In our study, the efficacy assessment was performed by patients at each follow-up visit using the subjective score provided by the results perceived after treatment. This information is important because patient's perception helps us improve the procedures, the explanation provided before starting the treatment, and expectations about results. Mean assessment of our patients was higher in the group treated for bromhidrosis, where 100% of patients perceived the treatment as positive, vs.

79.06% of patients treated for hyperhidrosis that perceived the treatment had provided them with some improvement. The differences may be due to the difference in the number of patients in each group.

Despite that the subjective assessments performed in our study don't use the same scale as those previously described, global results are similar and provide a guideline for the degree of satisfaction perceived by patients, which is translated in treatment effectiveness. If we average the data obtained from the studies by Glaser et al.[10], and Lupin et al. [11], at the same visits than our study (1, 3, 6 and 12 months), mean efficacy results were 74.75% for Glaser et al. and 96.55% for Lupin et al. If we compared them with the average of the subjective efficacy value obtained by patients in our study, which was 79.06%, we see that the number is similar to that obtained in the study with a larger number of patients.

For the treatment of bromhidrosis, in the study by Hong et al. [9], 68.55% of patients assessed their odor after treatment as imperceptible vs. 90.9% of patients in our study that assessed treatment as having fulfilled their expectations.

One limitation of the study was that HDSS was not assessed throughout the study, only in the baseline. This fact has made it not possible to compare this parameter with other investigations.

After assessing the study results, we considered that the treatment of hyperhidrosis and/or bromhidrosis with microwave technology is efficient and has lasting effects. Patient satisfaction with the procedure is high, and adverse events are usually temporary and well tolerated. This technology provides an alternative, lasting, non-invasive therapeutic modality. Despite the good results obtained - clinical as well as concerning patients' level of satisfaction - more studies should be conducted to assess the duration of the treatment effects in time in order to design the best protocol for the maintenance of said results.

Likewise, given our experience with both treatments and considering the results, we believe that the microwave treatment may be the most appropriate due to its durability and cost-benefit ratio compared with axillary botulinum toxin.

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Assessment of the superior turbinate pneumatization and concomitant nasal pathologies on computed tomography

Süperior türbinat pnömatizasyonu ve eşlik eden nazal patolojilerin bilgisayarlı tomografi ile değerlendirilmesi

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Abstract

Aim: Knowledge of the anatomical variations of the nasal cavity is extremely important for the safety and ease of endoscopic sinus surgery applications. The aim of the current study was to evaluate the incidence and uni/bilaterality of superior nasal turbinate pneumatization (STP). In addition, we aimed to investigate the frequency of middle turbinate pneumatization (MTP), nasal septum deviation (NSD) and paradoxical middle concha (PMC), and to relate the presence of these pathologies to the presence of STP.

Methods: We retrospectively reviewed the images of 358 consecutive patients who undertaken paranasal sinus computed tomography within five months' time in our institution. The presence and uni/bilaterality of the STP and MTP as well as the presence of NSD and PMC were noted. The relation of the STP with MTP, NSD and PMC were evaluated. Besides, the relationship between nasal variations and gender and age was evaluated.

Results: Of 358 patients, 105 (29.3%) had STP with 51 (48.6%) being bilateral and the remaining 54 (51.4%) being unilateral. The number of patients with accompanying MTP, NSD and PMC were 84 (80%), 63 (60%) and 32 (30.5%), respectively. No significant relationship between STP with NSD or PMC was recorded. However, STP significantly associated with MTP. We also noted that the patients with either STP or MTP were significantly younger than those without STP or MTP.

Conclusion: The knowledge of the variations of the structures that determine the nasal cavity anatomy and how often these variations are seen will enable the endoscopic surgical procedures to be performed easily and safely.

Keywords: Paranasal sinuses, Computed tomography, Anatomical variation, Pneumatized turbinate

Öz

Amaç: Endoskopik sinüs cerrahi uygulamalarının emniyeti ve kolaylığı yönünden nazal kavitenin varyasyonlarının bilinmesi son derece önemlidir. Bu çalışmanın amacı, üst türbinat havalanmasının (ÜTH) sıklık ve tek/çift taraflılığının değerlendirilmesidir. Yanı sıra, orta türbinat havalanması (OTH), nazal septum deviasyonu (NSD) ve paradoksal orta konka (POK) sıklıklarının saptanarak ÜTH ile ilişkilendirilmesi de amaçlanmıştır.

Yöntemler: Retrospektif olarak, ünitemizde beş ay içinde paranazal sinüs bilgisayarlı tomografisi elde olunan ardışık 358 hastanın inceleme kesitleri değerlendirildi. ÜTH ve OTH varlığı ve tek/çift taraflılığı ile NSD ve POK varlığı kaydedildi. ÜTH'nın MTH, NSD ve POK ile ilişkisi değerlendirildi. Yanı sıra, nazal varyasyonların cinsiyet ve yaşla ilişkisi değerlendirildi.

Bulgular: Çalışma grubunu oluşturan 358 hastanın, 51'i (%48,6) çift taraflı ve geri kalan 54'ü (%51,4) tek taraflı olmak üzere 105 tanesinde ÜTH mevcuttu. ÜTH'na eşlik eden OTH, NSD ve POK olgularının sayısı sırasıyla 84 (%80), 63 (%60) ve 32 (%30,5) idi. ÜTH ile NSD ve POK arasında anlamlı ilişki saptanmadı. Ancak, ÜTH ile OTH arasında anlamlı birliktelik saptandı. Ayrıca, ÜTH veya OTH mevcut olan hastaların, mevcut olmayanlara kıyasla daha genç olduğunu kaydedildi.

Sonuç: Nazal kavite varyasyonlarının ve bunların sıklıklarının bilinmesi, endoskopik cerrahi prosedürlerin kolay ve emniyetli uygulanmalarını sağlayacaktır.

Anahtar kelimeler: Paranazal sinüsler, Bilgisayarlı tomografi, Anatomik varyasyon, Türbinat havalanması

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Introduction

The rapid developments in endoscopic sinus surgery techniques and the increase in the use of this intervention method raised the importance of the nasal as well as paranasal anatomic variations. Coronal computed tomography (CT) sections are extremely informative in examining the nasal cavity prior to the endoscopic intervention because these sections demonstrate the same regions as seen during endoscopic examination [1].

Concha bullosa is generally considered as pneumatization of the middle turbinate, but it can also be seen in superior and lower turbinates [2]. The expansion of the turbinate(s) as well as the other pathologies causing differences in the angle of the walls of the nasal cavity and/or resulting in the nasal volumetric differences are extremely important in delineating the interventional pathway during endoscopic surgery. The aim of the current study was to evaluate the incidence and uni/bilaterality of superior nasal turbinate pneumatization (STP). In addition, we aimed to investigate the frequency of the pathologies such as middle turbinate pneumatization (MTP), nasal septum deviation (NSD) and paradoxical middle concha (PMC), and to relate the presence of these pathologies to the presence of STP.

Materials and methods

Patient population and study design

The approval of the institutional review board was received before the execution of this work started. Radiological records of a total of 358 patients who underwent CT of the paranasal sinuses between January 1, 2019 and June 1, 2019 because of headache, nasal obstruction, anosmia, facial pain or facial trauma were evaluated retrospectively. There were 195 men and 163 women with a mean age of 36.8 years (range: 17 to 69). Imaging was performed using a 128-slice CT scanner (Optima CT 660, GE Healthcare System, Milwaukee, USA), (120 kV; 150 mAs; slice thickness = 0.5 mm; FOV = 18-24 cm).

The CT images of the paranasal sinuses of all patients were examined in terms of the presence and uni/bilaterality of STP. The cases with MTP, NSD and PMC were noted (Figure 1). The patients' age and gender were also recorded. Two experienced radiologists reviewed the CT images independently. In the cases of whom a discrepancy occurred in the interpretations of the images, a common re-examination was performed and the final decisions were made by consensus.

Statistical analysis

The normality of distribution of continuous variables was tested by Shapiro-Wilk test. Mann Whitney U test was used to compare 2 independent groups for non-normal data. Chi-square test was performed to investigate the relationship between categorical variables and Odds ratio and 95% confidence intervals were calculated to show effect size. Statistical analysis was performed with SPSS for Windows version 24.0 and a P value < 0.05 was accepted as statistically significant.

Results

The overall prevalence of uni/bilateral STP, uni/bilateral MTP, NSD and PMC in our study population is summarized in table 1. Of 358 patients, 105 (29.3%) had STP. Of these, 51 (48.6%) had bilateral and the remaining 54 (51.4%) had unilateral STP. The prevalence of uni/bilateral MTP, NSD and PMC in cases with STP in our study population is summarized in table 2.

Table 1: The findings of the overall study population

		n	%
Superior turbinate pneumatization	Positive	105	29.3
	Unilateral positive	54	15.1
	Bilateral positive	51	14.2
	Negative	253	70.7
Middle turbinate pneumatization	Positive	186	52.0
	Unilateral positive	97	27.1
	Bilateral positive	89	24.9
	Negative	172	48.0
Nasal septum deviation	Positive	190	53.1
	Negative	168	46.9
Paradoxical middle concha	Positive	95	26.5
	Negative	263	73.5

Table 2: The findings of 105 patients with superior turbinate pneumatization

		Superior turbinate pneumatization					*P*-value
		Positive		Negative			
		N	%	N	%	OR [95% CI]	
Middle turbinate pneumatization	Positive	84	80.0	102	40.3	5.92 [3.45-10.16]	0.001*
	Negative	21	20.0	151	59.7	1 (reference)	
Nasal septum deviation	Positive	63	60.0	127	50.2	1.49 [0.94-2.36]	0.091
	Negative	42	40.0	126	49.8	1 (reference)	
Paradoxical middle concha	Positive	32	30.5	63	24.9	1.32 [0.79-2.19]	0.277
	Negative	73	69.5	190	75.1	1 (reference)	

*Significant at 0.05 level, Chi-square test, OR: Odds ratio, CI: Confidence Interval

The number of patients with accompanying MTP, NSD and PMC were 84 (80.0%), 63 (60.0%) and 32 (30.5%), respectively. There was a significant association between the presence of STP and MTP. The likelihood of the presence of MTP in patients with STP is 5.92 times higher than those without STP. However, no significant relation of STP with NSD or PMC was recorded (Figures 2, 3).

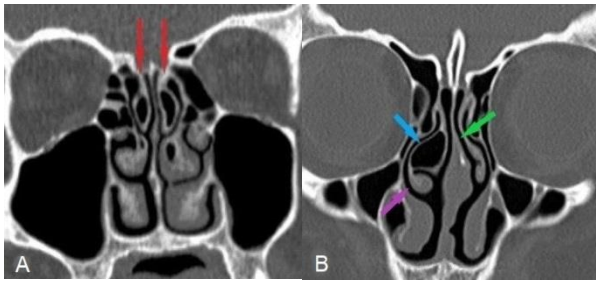

Figure 1: Coronal computed tomography sections of two different patients. (A) Bilateral superior nasal turbinate pneumatization (red arrows). (B) Unilateral middle turbinate pneumatization (blue arrow), nasal septum deviation (green arrow) and paradoxical right middle concha (purple arrow)

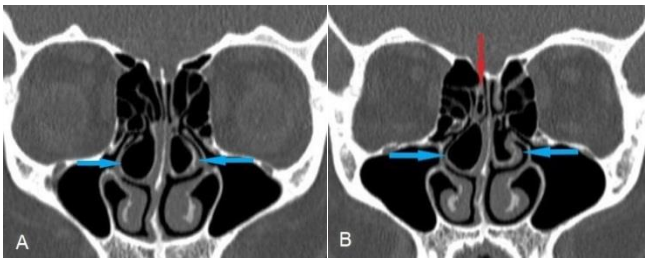

Figure 2: Consecutive coronal computed tomography sections of a 52-year-old woman demonstrating unilateral superior nasal turbinate pneumatization (red arrow) and bilateral middle turbinate pneumatization (blue arrows)

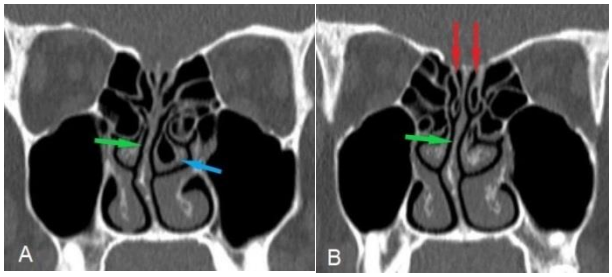

Figure 3: Consecutive coronal computed tomography sections of a 20-year-old man demonstrating bilateral superior nasal turbinate pneumatization (red arrows), unilateral middle turbinate pneumatization (blue arrow) and nasal septum deviation (green arrows)

No significant relationship between any of the nasal variations and gender was noted (Table 3). The relationship between nasal variations and age is demonstrated in table 4. It is shown that the patients with either STP or MTP were significantly younger than those without STP or MTP. For each age increase in patient age, a 2% increase in both STP and MTP frequency was recorded. There was no significant relationship between age and NSD or PMC.

Table 3: The relationship between nasal variations and gender

		Gender				*P*-value
		Female		Male		
		N	%	N	%	
Superior turbinate pneumatization	Positive	46	28.2	59	30.3	0.674
	Negative	117	71.8	136	69.7	
	OR [95% CI]	1 (reference)		0.91 [0.57-1.43]		
Middle turbinate pneumatization	Positive	90	55.2	96	49.2	0.259
	Negative	73	44.8	99	50.8	
	OR [95% CI]	1 (reference)		1.27 [0.84-1.93]		
Nasal septum deviation	Positive	89	54.6	101	51.8	0.596
	Negative	74	45.4	94	48.2	
	OR [95% CI]	1 (reference)		1.12 [0.74-1.69]		
Paradoxical middle concha	Positive	44	27.0	51	26.2	0.858
	Negative	119	73.0	144	73.8	
	OR [95% CI]	1 (reference)		1.04 [0.65-1.67]		

*Significant at 0.05 level, Chi-square test, OR: Odds ratio, CI: Confidence Interval

Table 4: The relationship between nasal variations and age

		N	Mean (SD)	Median (Min-Max)	OR [95% CI]	*P*-value
Superior turbinate pneumatization	Positive	105	33.86 (12.87)	32 (18-65)	0.98 [0.96-0.99]	0.006*
	Negative	253	38.08 (13.22)	38 (17-69)	1 (reference)	
Middle turbinate pneumatization	Positive	186	35.28 (12.93)	33 (18-67)	0.98 [0.96-0.99]	0.025*
	Negative	172	38.52 (13.39)	39 (17-69)	1 (reference)	
Nasal septum deviation	Positive	190	35.93 (13.01)	34 (17-69)	0.99 [0.97-1.01]	0.218
	Negative	168	37.86 (13.45)	38 (18-67)	1 (reference)	
Paradoxical middle concha	Positive	95	35.96 (13.46)	34 (18-69)	0.99 [0.97-1.01]	0.399
	Negative	263	37.16 (13.17)	37 (17-67)	1 (reference)	

*Significant at 0.05 level, Chi-square test, OR: Odds ratio, CI: Confidence Interval

Discussion

We retrospectively reviewed the paranasal sinus CT images of 400 consecutive patients and found that, of the overall study group, 105 (29.3%) had STP. Of these, 51 (48.6%) had bilateral and the remaining 54 (51.4%) had unilateral STP. We found a significant association between the presence of STP and MTP. No significant association between any nasal variation and gender was recorded. However, it is shown that patients with either STP or MTP were significantly younger than those without STP or MTP.

Regulating the nasal air flow by heating, humidifying and filtrating the inhaled air, nasal turbinates play a critical role in maintaining the normal nasal functions [3]. They can easily be injured during endoscopic surgery resulting in postoperative hyposmia caused by the olfactory neuroepithelium damage [4]. The clinical importance of the knowledge concerning the presence of STP is not limited to its significance regarding the endoscopic interventions. They are shown to cause headaches, even in the absence of sinonasal inflammation [5]. Furthermore, they are accused of causing stenosis or obstruction of the superior meatus or sphenoid sinus ostium [1]. According to previous studies, the incidence of STP ranges between 12.2 and 50%. And the range of its being bilateral is reported to be 38.9%-44% [6-8]. In accordance with the data range determined in previous studies, we found STP in 29.3% of our study population. However, being present in 48.6% of the patients, bilaterality of STP in our population was higher than that in those of the previous studies.

MTP, which is also referred to as bullous middle turbinate was firstly described as a transformation of the anterior part of the middle turbinate into a bubble, by Santorini [9]. This type of pneumatization is considered to represent a variation of ethmoid air cell development, not the outcome of an intranasal process [9,10]. According to the previous studies, the incidence of MTP ranges from 14 to 53%, and the incidence of bilateral MTP has been reported to be between 45 and 61.5% [11-13]. In accordance with the previous literature, the prevalence of MTP was 52% and 47.8% of MTP cases were bilateral in the current study population. There was a significant association between the presence of STP and MTP. Moreover, we showed that the likelihood of the presence of MTP in patients with STP is about six times higher than those without STP. This association implies that, the development of MTP could induce the pneumatization of the superior turbinate(s) by changing the air circulation dynamics of the nasal cavity as well as the paranasal sinuses.

We recorded no significant association between any nasal variation and gender. On the other hand, according to our results, the patients with either STP or MTP were significantly younger than those without STP or MTP. We speculate that the amount of pneumatization of turbinates may vary depending on age and may be extinguished to some extent with aging.

NSD means that the nasal septum is located outside the midline and plays an important role in functional nasal breathing. It may cause symptoms such as sleep apnea, facial pain, nasal bleeding, and difficulty in breathing and impairment in smell [14]. Previous studies demonstrated that there is no significant association between STP and NSD [6,15]. We found NSD in 53.1% of our study population, and in consistence with the previous data, we found no statistically significant relation between STP and NSD. PMC is characterized by the convex curvature of the medial concha towards the lateral side and may cause nasal obstruction in cases with an extreme curve. The previously reported prevalence of PMC varies between 3 and 26.9% [16-18]. Being 26.5%, the prevalence of PMC we recorded falls within this frequency range.

The major limitation of the current study is that we did not evaluate the relation of the anatomic nasal variations with the development of sinonasal infections. The second important limitation of the study is the relatively small number of the study population. Further comprehensive studies adopting a clinico-radiological approach are needed to reach accurate and inclusive comments regarding the prevalence and clinical significance of the nasal turbinate pneumatization as well as the other anatomic nasal variations.

In conclusion, the STP, either unilateral or bilateral, are nasal anatomical variations which can be present in up to half of the population. The results of the current study revealed that, there is a significant relationship between the frequency of STP and MTP. Coronal computed tomography sections of paranasal sinuses are of particular importance for endoscopic surgeons in delineating their pathway in the nasal cavity during interventions. The knowledge of the variations of the structures that determine the nasal cavity anatomy and how often these variations are seen will ensure that endoscopic surgical procedures are performed easily and safely.

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Laparoscopic management of cornual pregnancy: A case report

Kornual gebelikte laparoskopik tedavi: Olgu sunumu

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Abstract

The incidence of cornual or interstitial pregnancy is approximately 2% of all pregnancies. Interstitial pregnancy is one of the rare form of ectopic pregnancies, with 1-6% of all ectopic pregnancies. In our case report, we present successful laparoscopic resection of a cornual pregnancy with positive fetal cardiac activity and laparoscopic suturing of cornu uteri. A 26-year-old pregnant; gravida 2, para 0, abortus 1; was admitted with a complaint of left lower quadrant abdominal pain. An ultrasound examination was performed. The ultrasound examination revealed a 4-cm ectopic gestational sac with positive cardiac activity in the left adnexa. Laparoscopy was planned. A left uterine approximately 3x4 cm cornual pregnancy was observed, under direct visualization, one 5-mm coagulating dissector was used to perform the resection and seal of the cornu uteri. After the sealing, two times laparoscopic suturing was applied. Detecting interstitial pregnancy is more difficult than revealing other ectopic pregnancy types. Severe hemorrhage could occur during the resection of the cornu uteri. Therefore, a laparoscopic approach should only be attempted if the surgeon is well skilled in laparoscopic technique, and has the capability to convert the operation quickly to a laparotomy.

Keywords: Laparoscopy, Ectopic pregnancy, Cornual pregnancy

Öz

Kornual veya interstisyel gebelik insidansı tüm gebeliklerin yaklaşık %2'sidir. İnterstisyel gebelik, tüm ektopik gebeliklerin %1-6'sı ile nadir görülen ektopik gebeliklerden biridir. Olgumuzda, pozitif fetal kardiyak aktivite gözlenen kornual ektopik olgusunun başarılı bir şekilde laparoskopik rezeksiyonu ve kornu uterinin laparoskopik sütüre edildiği olguyu sunuyoruz. 26 yaşında hamile; gravida 2, para 0, abort 1; sol alt kadran karın ağrısı şikayeti ile başvurdu. Ultrason muayenesi yapıldı. Ultrason muayenesinde sol adnekste pozitif kardiyak aktivite gösteren 4 cm'lik bir ektopik gebelik kesesi saptandı. Laparoskopi planlandı. Solda uterin kornuda, yaklaşık 3x4 cm kornual gebelik görüldü, 5 mm'lik bir koter disektör, cornu uteri'nin rezeksiyonu ve mühürlenmesi için kullanıldı. Sonrasında, iki kez laparoskopik dikiş atıldı. İnterstisyel gebeliği tespit etmek, diğer ektopik gebelik tiplerini ortaya koymaktan daha zordur. Cornu uteri'nin rezeksiyonu sırasında ciddi kanamalar görülebilir. Bu nedenle, laparoskopik bir yaklaşım, ancak cerrah laparoskopik teknikte uzmansa ve operasyonu hızlı bir şekilde laparotomiye dönüştürme yeteneğine sahipse denenmelidir.

Anahtar kelimeler: Laparoskopi, Ektopik gebelik, Kornual gebelik

Introduction

The interstitial portion of the fallopian tube is the proximal portion that is within the muscular wall of the uterus. It is 0.7 mm wide and 1 to 2-cm long [1]. The incidence of cornual or interstitial pregnancy is approximately 2% of all pregnancies. Interstitial pregnancy is one of the rare form of ectopic pregnancies, with 1-6% of all ectopic pregnancies [2]. It tends to rupture at a more advanced gestation compared to tubal ectopic pregnancy. It is not easy to ascertain exact localization of the cornual pregnancy accurately with the help of ultrasound. Since majority of the ectopic pregnancies have tendency to occur in ampullar region, generally preoperatively cornual pregnancies are misdiagnosed as ampullar ectopic pregnancies [3].

Current surgical procedure for tubal ampullar ectopic pregnancies are generally laparoscopy and then laparotomy [4]. However in case of cornual pregnancy, surgeons have reluctance to use laparoscopy, because of high risk of bleeding and difficulty of laparoscopic suturing.

In our case report, we present successful laparoscopic resection of a cornual pregnancy with positive fetal cardiac activity and laparoscopic suturing of cornu uteri.

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Case presentation

A 26-year-old pregnant; gravida 2, para 0, abortus 1; was admitted to our clinic with a complaint of left lower quadrant abdominal pain. An ultrasound examination was performed. The ultrasound examination revealed a 4-cm ectopic gestational sac, crown rump length 21-mm, with positive cardiac activity in the left adnexa. Regarding the findings, emergent laparoscopy was planned. The first, 10-mm trocar port for the laparoscope was entered by umbilicus. A left uterine cornual approximately 3x4 cm bulging ectopic sac was observed. The second and third 5-mm ancillary trocar ports were entered in the right and left lower quadrants. Cornual pregnancy was aspirated and approximately 3-cm fetus was attached to the aspirator, as shown in figure 1. Under direct visualization, one 5-mm coagulating dissector (Ligasure, Covidien ®) was used to perform the resection and seal of the cornu uteri. After the sealing, two times intracorporeal laparoscopic suturing with 1-0 Vicryl (Ethicon, Cincinnati, OH, USA) was applied and bleeding was completely taken under control, as shown in figure 2. The duration of the operation was approximately one hour.

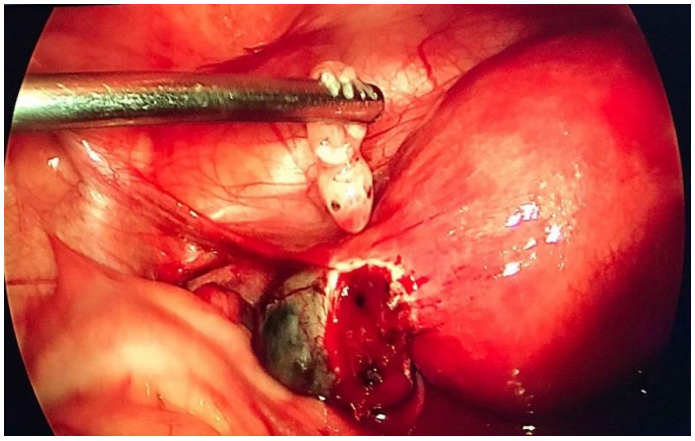

Figure 1: Ruptured left cornual pregnancy, the fetus attached to the aspirator

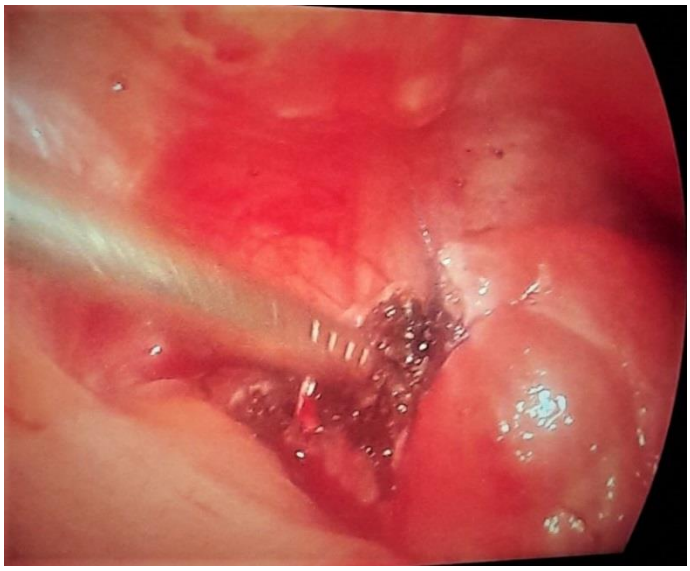

Figure 2: The sutured left cornu uteri

Estimated blood loss was 100 ml and the patient recovered without complication. The day after the operation, she was discharged uneventfully. Serum β-human chorionic gonadotrophin concentration decreased from 84,790 mIU/ml at the time of the operation to <1.5 mIU/ml in 4 weeks. The written consent was obtained from the patient presented in the study.

Discussion

Detecting interstitial pregnancy is more difficult than revealing other ectopic pregnancy types, since the gestational sac, located in the myometrium, is isolated from other pelvic organs, so it presents itself as grave hemorrhage leading to hypovolemic shock resulting from rupture of uterus rather than localized pelvic pain as seen in other types [5,6].

With the help of ultrasound, incomplete or asymmetrical myometrium surrounding eccentric located gestational sac sign is a unique diagnostic finding for interstitial pregnancy [7]. However this is not always easy.

Although cornual pregnancies have traditionally been treated with hysterectomy or cornual resection, several more conservative techniques have recently become available [8]. In the case of an early and asymptomatic ectopic gestation, methotrexate has been shown to be an effective treatment by Sel et al [5] previously. A ruptured interstitial pregnancy is a medical emergency that requires an immediate surgical intervention either by laparoscopy or laparotomy to stop the bleeding and remove the pregnancy [9].

In Selma et al's [10] series, there was a tendency to perform laparoscopic wedge resection instead of cornuostomy because of the perception that extirpative surgery would result in fewer persistent cornual pregnancies. We also performed wedge resection and laparoscopic suturing in our case, to make it certain that no bleeding would occur and in order to prevent rupture of future pregnancies, since uterine rupture in future pregnancy following salpingectomy for interstitial pregnancy has been reported in the literature [11].

Laparoscopy is the gold standard for treatment in ectopic pregnancy, laparotomy is considered to be outdated. Even in women with significant hemoperitoneum, laparoscopic surgery can be safely conducted by experienced laparoscopic surgeons if hemodynamic stability is achieved by perioperative management [10].

However, severe hemorrhage could occur during the resection of the cornu uteri. Therefore, a laparoscopic approach should only be attempted if the surgeon is well skilled in laparoscopic technique, and has the capability to convert the operation quickly to a laparotomy. When these conditions are met, laparoscopy provides several advantages over laparotomy: fewer post-operative hospital days, faster return to normal activity, and decreased health care costs [8].

Cornual ectopic pregnancy is an uncommon case to be faced in obstetrics practice, albeit comprises grave risk to the pregnant women when it happens. Therefore, it is prudent to consider this diagnosis in case of an atypically localized gestational sac observed with ultrasound.

In recent years, laparoscopic management of any kind of surgery, of course with the exception of cesarean of intrauterine viable fetus, is possible. As surgeons get experienced, laparoscopy would be conventional surgery and laparotomy would be a historical practice.

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A rare location for osteoid osteoma on the foot: A case report

Ayakta osteoid osteoma için nadir bir yer: Olgu sunumu

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Abstract
Osteoid osteoma (OO) is benign small neoplasm of the bone that accounts for 11% of all benign tumors and 3% of all primary benign tumors. Usually they are located at diaphyseal and metaphyseal regions of long bones, but foot lesions are rare. Metatarsal osteoid osteoma's are quite rare. We present a 23 years old male with the complaints of ongoing swelling localized at fifth finger of right foot for 1 year. Preoperative osteoid osteoma diagnosis was made and lesion was removed with curettage and burring.
Keywords: Osteoid osteoma, Metatarsi, Curettage, Foot

Öz
Osteoid osteoma (OO), tüm iyi huylu kemik tümörlerinin %11'ini ve tüm primer iyi huylu tümörlerin %3'ünü oluşturan kemiğin benign küçük neoplazmıdır. Genellikle uzun kemiklerin diyafiz ve metafiz bölgelerinde bulunurlar, ancak ayak lezyonları nadirdir. Metatarsal osteoid osteomalar oldukça nadirdir. Bu çalışmamızda sağ ayak beşinci parmağında, 1 yıl boyunca l devam eden şişlik şikayeti olan 23 yaşında bir erkek hastayı sunmayı amaçladık. Hastaya preoperatif osteoid osteoma tanısı konuldu, küretaj ve burleme işlemiyle lezyon alındı.
Anahtar kelimeler: Osteoid osteoma, Metatars, Küretaj, Ayak

Introduction

Osteoid osteoma (OO) is benign small neoplasm of the bone that accounts for 11 % of all benign tumors and 3% of all primary benign tumors [1]. The most frequent localization of OO is the diaphyseal and metaphyseal regions of long bones, especially the femur and tibia [1]. Approximately 10% of all OO is seen at foot especially at neck of the talus [2]. Other locations of the foot are rare occurrence. We want to present a case of metatarsal OO in this article.

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Case presentation

A 23 years old male otherwise healthy patient admitted to our outpatient clinic with the complaints of ongoing swelling localized at fifth finger of right foot for 1 year. The patient did not complain of pain and also had no other clinical findings except edema. He was indeed complaining about the swelling on the lateral of the foot expanding regularly within 1 year. There was significant swelling on the proximal metaphysis of fifth metatarsi at physical examination (Figure 1). He expressed difficulty while wearing his shoe. There was accompanying tenderness and mild increase in local temperature. Preoperative plain radiographs demonstrated a lytic bone lesion with a sclerotic rim at proximal of metaphysis the fifth metatarsi. Lesion was elevated the periosteum of the metatarsal and went out of cortical bone (Figure 2). Informed consent was obtained from the patients included in the study.

Blood tests and bone scan was made since OO's clinical presentation can mimic osteomyelitis or inflammatory arthritis. Infection indicators like sedimentation rate, C-reactive protein, and leukocyte values were within normal ranges. Tc^{99m} bone scan revealed diffuse intense uptake at fifth metatarsi. Magnetic resonance imaging (MRI) scan was obtained for differential diagnosis. MRI showed rounded nidus along the lateral border of fifth metatarsi bone marrow and soft tissue edema in fifth metatarsi (Figure 3).

Preoperative osteoid osteoma diagnosis was made. The patient was informed about the procedures and an informed consent form was signed. A longitudinal incision on the lateral side of the fifth metatarsi was made for surgical exposure. OO with significant nidus was remarkably seen at fifth metatarsi (Figure 4). Intraoperative frozen section of the surrounding soft-tissue revealed no malignancy. Intraosseous lesion was removed with curettage and burring. Lesion was sent for culture and pathological examination; osteoid osteoma diagnosis was confirmed (Figure 5). The patient did not feel any pain during preoperative and later postoperative process except the early postoperative period. Our patient healed with no complication after a 2 year follow up period.

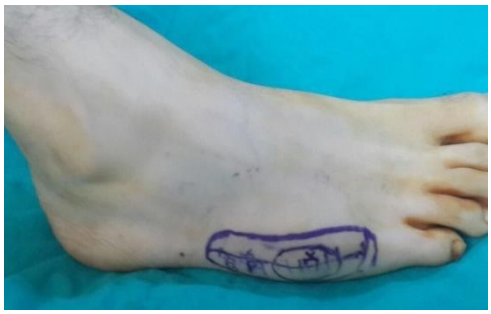

Figure 1: There was significant swelling on the proximal metaphysis of fifth metatars at physical examination

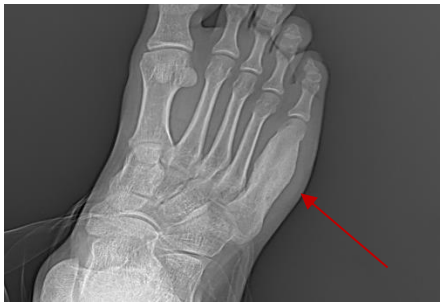

Figure 2: Lesion was elevated the periosteum of the metatarsal and went out of cortical bone

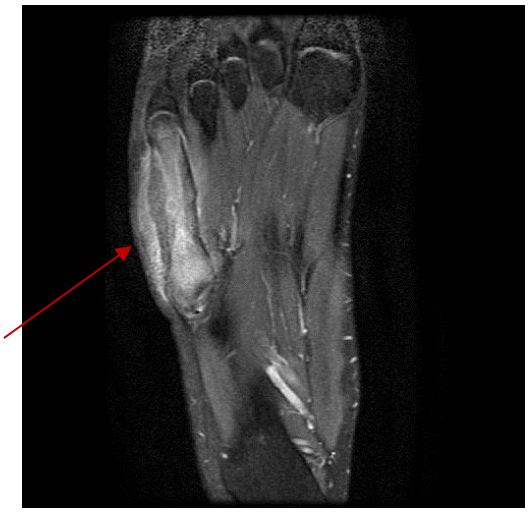

Figure 3: MRI showed rounded nidus along the lateral border of fifth metatars bone marrow and soft tissue edema in fifth metatarsi

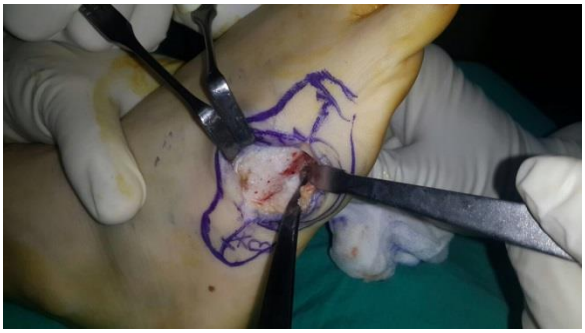

Figure 4: Significant nidus was remarkably seen at fifth metatars

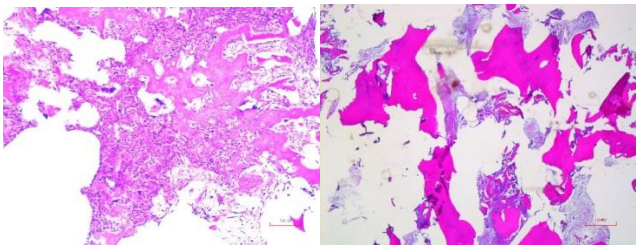

Figure 5: Pathological examination of the removed nidus

Discussion

We presented a case of an uncommon located osteoid osteoma. Foot is a rare location for OO. Talar neck comparatively the most common (3.4%) region for foot OO [2]. Metatarsal osteoid osteoma is quite rare with the incidence of 1.7% [2]. Spencer et all presented a case report about 24 -year old female patient who was diagnosed as fifth metatarsal's osteoid osteoma. Their radiological studies revealed erosion of the medial aspect of the head of the fifth metatarsal with destruction of the cortical margin. Patient healed with complete relief after removing of the lesion with curettage and burring [3].

Classical history of osteoid osteoma is progressive throbbing, disturbing pain that relieve with non-steroidal anti-inflammatory drugs and worse at night. It is so severe that wakes the patient up. Nocturnal pain is unique among bone tumors [4]. The reason for timing of pain is unknown but there are 2 explanations about the reason of pain. First, prostaglandin E2 ($PGE_{2)}$ is responsible for the pain by vasodilatation and by affecting pain signals [5]. Nidus osteoblasts produce cyclooxygenase-2 enzyme which is key for production of $PGE_{2.}$ PGE_2 concentration in the nidus may be 1000-fold increase in concentration [6-8]. Second pain reason is nerve fibers in the nidus. They are established especially in the perifocal reactive zone [4]. Reactive zone is a loose fibrovascular tissue with nerve

fibers in. Tension at this reactive zone, which should be loose, results in with pain. Our patient did not show classical osteoid osteoma pain history. He didn't have nocturnal pain and even severe pain. All his complaints were about the fear of malignant tumor because of severe swelling and enlargement. We think that osteoid osteoma unloaded its content by elevating the periosteum of the metatarsal and went out of cortical bone. This mechanism prevented pain but swelling occurred.

Differential diagnosis of osteoid osteoma is with bone abscess, solitary enostosis, osteomyelitis, sclerosing osteitis, syphilis of bone, early-stage Ewing's sarcoma, glomus tumor, or stress fracture. When there is confusion about diagnosis blood tests, bone scan and either computerized tomography (CT) or MRI must be performed. We also planned blood test, bone scan and MRI scan for our case to differentiate the diagnosis with osteomyelitis.

Optimal treatment for osteoid osteoma is surgery. Lesion is either excised or ablated because pain disturbs the patient's much, even wake them up at night. Nevertheless, there are numerous publications that state spontaneous regression of untreated OO during an average of 6 years [9]. Lesions closer to bone cortex and younger patients has higher chance of spontaneous regression [1]. If the patient tolerates pain with using non-steroidal anti-inflammatory drugs conservative treatment may be a choice for the patient. But if there is a severe pain that affects patient's participation in social life and psychological state then there is an indication for surgery.

The nidus, the source of pain, must be removed completely for pain relief. Most important step in cure is to determine the exact localization of nidus. Preoperative radiography or CT, preoperative CT-guided needle marking or perioperative fluoroscopic scanning must be done for exact localization. Occasionally in very rare cases, like ours, nidus can be seen visible even macroscopically.

En-bloc resection and removing with curettage and burring techniques are most common surgical methods [1]. Although wide local excision has greater advantages like assurance that all the nidus is removed, it is also more invasive. Also, success rates are very high with careful local curettage and burring technique [10]. Less invasive techniques like radiofrequency ablation treatment [11], CT-guided percutaneous nidus removal [10] are also favorable techniques for nidus removal.

Conclusion

Osteoid osteomas are common benign lesions but foot lesions are rare. Metatarsal osteoid osteoma is quite rare entity. Because of their presentations in uncommon location should be kept in mind as a reason of foot pain. It is possible to get high success rates with careful surgery to well-localized nidus in the cases which conservative treatment does not benefit.

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Spontaneous splenic hematoma due to anticoagulant treatment: A case report

Antikoagülan tedaviye bağlı spontan splenik hematom: Olgu sunumu

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Abstract
Splenic injury is mostly associated with trauma, but spontaneous splenic injury has been associated in various systemic diseases. A 46-year-old male patient was admitted to the emergency department with epigastric pain and tenderness in the left upper quadrant. There was no history of trauma, but he was using oral anticoagulant treatment. Contrast-enhanced computed tomography imaging revealed a subcapsular hematoma of the spleen. Oral anticoagulation was antagonized with vitamin K and the patient was discharged in good condition after 3 days of clinical observation. Non-traumatic splenic rupture is a rare complication of oral anticoagulation.
Keywords: Spleen, Oral anticoagulant, Non-traumatic splenic hematoma

Öz
Splenik yaralanma normalde travma ile ilişkilidir, ancak çeşitli sistemik hastalıklarda spontan splenik rüptürü tanımlanmıştır. 46 yaşında erkek hasta acil servise epigastrik ağrı ve sol üst kadranda hassasiyet ile başvurdu. Travma öyküsü yoktu, oral antikoagulan kullanımı mevcuttu. Kontrastlı bilgisayarlı tomografi görüntülemesi dalağın büyük bir subkapsüler hematomunu ortaya çıkardı. Oral antikoagülasyon K vitamini ile antagonize edildi ve hasta 3 günlük klinik gözlemden sonra iyi durumda taburcu edildi. Travmatik olmayan splenik rüptür, oral antikoagülasyonun nadir görülen bir komplikasyonudur.
Anahtar kelimeler: Dalak, Oral antikoagulan, Non-travmatik dalak hematomu

Introduction

The spleen is usually a ruptured organ after blunt abdominal trauma. Unlike traumatic splenic rupture, spontaneous (atraumatic) splenic rupture is a rare and life-threatening condition. Little is known about the characteristics, incidence and etiology of patients. The etiology of atraumatic spleen rupture is examined in six different categories. These are infectious, neoplastic, inflammatory, congenital or structural, iatrogenic and finally idiopathic [1,2]. In this paper, a patient with spontaneous splenic rupture who admitted to the emergency department with abdominal pain was presented and discussed in the light of current literature.

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

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Case presentation

A 46-year-old male patient presented to our emergency department with abdominal pain. He had a history of mitral valve replacement 15 years ago and coumadin use afterwards. At the initial presentation, hematocrit was 25.7% and hemoglobin was 8.5 g/dl. INR value was 7.1. Abdominal ultrasound and abdominal computed tomography examinations revealed a lesion compatible with hematoma extending approximately 6 cm from the upper pole to the middle pole (Figure 1). The patient was diagnosed with non-traumatic subcapsular spleen hematoma. Anticoagulant treatment was discontinued and vitamin K was administered. He was followed up with daily INR and abdominal examination. In the follow-up, when abdominal findings were normal and INR value decreased to 2.5, he was discharged with low molecular weight heparin treatment as anticoagulant for 10 days to prevent the risk of thromboembolism. Anticoagulant therapy was continued with coumadin according to INR results after heparin treatment. One month later, control abdominal tomography showed regression in the hematoma.

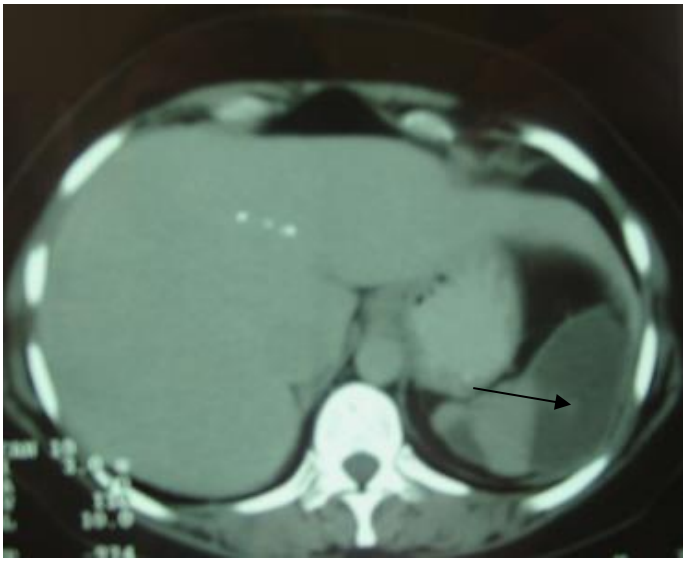

Figure 1: Abdominal computed tomography of the patient showing the hematoma in the spleen (arrow)

Discussion

Subcapsular hematoma of the spleen is one of the rare complications of anticoagulant therapy. There may be no other complaint in the clinic except for ambiguous abdominal pain. Anticoagulants, especially coumadin sodium, are used in many fields of medicine. Bleeding complications such as intracranial, intraabdominal, intramural intestinal, rectus muscle sheath hematoma have been reported in the literature after anticoagulant use [3].

The most common cause of splenic rupture is trauma. The term atraumatic or spontaneous spleen rupture was first described by Orloff and Peskin in 1958 and identified four criteria for diagnosis. These include: absence of a history of trauma, absence of perisplenic adhesions to support previous traumas, absence of disease affecting the spleen, and microscopic and macroscopically natural spleen [2].

In our country, Gedik et al. [4] reported a series of seven cases (6 males, 1 female), and the most common cause of the etiology was malaria with four cases. Özsoy et al. [5] reported two cases of malaria. Malaria infection is known to be the most common etiology in tropical countries [6]. Malaria infections in Turkey, although greatly reduced in some endemic areas (south and southeast) are still visible. In patients living or traveling to these regions, if there are complaints of tremor and fever, it should be remembered in the differential diagnosis [7]. Patients with spontaneous splenic rupture show a similar clinical condition to those with traumatic splenic rupture. Abdominal pain, nausea, vomiting, dizziness and syncope symptoms may be seen in the left upper quadrant before the signs of shock [8-10]. In our case, abdominal pain was admitted to the emergency department with complaints of abdominal pain. Spontaneous splenic rupture cases often present with signs of hemorrhagic shock. Even in these cases, mortality was found to be high [4]. Total splenectomy was reported as 84.1%, organ-sparing surgery 1.2% and conservative approach 14.7% rates in the study of Renzulli et al. [3]. Other therapies other than total splenectomy are often recommended for non-neoplastic causes. In our case, lack of hemorrhagic shock findings and early surgical intervention due to rapid diagnosis was lifesaving.

Conclusion

Spontaneous splenic rupture is a rare patient group which is a rare condition for emergency physicians and requires high suspicion in diagnosis. Although there is no history of trauma, spleen rupture may occur in patients. Rapid diagnosis, aggressive resuscitation and early surgery when necessary are very important.

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