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DiGeorge syndrome (Chromosome 22q11.2 deletion syndrome): A historical perspective with review of 66 patients

DiGeorge Sendromu (Kromozom 22q11.2 delesyon sendromu): Altmış altı hastanın incelendiği tarihsel perspektif

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Abstract

Aim: Congenital heart defects (CHD) are the most common major birth defects in humans. Conotruncal cardiac defects (CCD) and aortic arch anomalies, the outflow tract anomalies of the heart, usually accompany dysmorphic syndromes. Di George Syndrome, deletion of 22q11.2, is one of the typical examples for this entity. Our study was designed to determine the frequency of 22q11.2 deletion in a retrospectively ascertained sample of patients with conotruncal cardiac defects and structural cardiac defects accompanying other clinical findings of 22q11.2 deletion syndrome.

Methods: A total of 66 patients (4 days-16.6 years; mean 38 months), 56 followed with the diagnosis of conotruncal cardiac defects and 10 having congenital cardiac defects other than conotruncal abnormalities participated to our study . All patients underwent karyotype and Fluorescence in Situ Hybridization (FISH) analysis for 22q11.2 deletion. After the detection of the deletion a follow up protocol was formed for the patients

Results: Five of all patients were found to have the deletion positive (7.6%). Four of them had conotruncal cardiac defects. All patients having 22q11.2 deletion had at least one abnormality of the syndrome other than cardiac problems. Facial dysmorphism and growth retardation were the most common features .Cognitive disability, feeding problems, hypocalcemia, psychiatric problems, immunity differences were the other associated problems. Parental evaluation yielded one mother to be a deletion carrier.

Conclusion: We suggest that 22q11.2 deletion must be explored in all newborns with selective conotruncal cardiac defects and with non- conotruncal cardiac defects accompanying the other anomalies of the syndrome. All deletion positive patients must be evaluated for the accompanying features of the syndrome with genetic counselling.

Keywords: 22q11.2 deletion, Conotruncal anomalies, Fluorescence in Situ Hybridization

Öz

Amaç: Doğumsal kalp hastalıkları insanlarda en sık görülen konjenital anomalilerdir. Kalbin çıkış yolu anomalileri olan konotrunkal kalp hastalıkları ve aort arkı anomalileri genellikle dismorfik sendromlara eşlik eder. 22q11.2 delesyon sendromu bu klinik durumun tipik örneklerindendir. Bu çalışma konotrunkal kalp anomalileri ve 22q11. 2 delesyon sendromunun diğer klinik bulgularının eşlik ettiği doğumsal kalp hastalıklarında 22q11.2 delesyon sıklığını araştırmak amacıyla planlanmıştır.

Yöntem: Yaşları 4 gün ile 16.6 yaş arasında değişen 56 konotrunkal kalp anomalili, 10 yapısal kalp anomalisi ile sendromun diğer klinik bulgularının eşlik ettiği 66 hasta çalışmaya katıldı. Tüm hastalara karyotip analizi uygulandı, Floresan in situ hibridizasyon yöntemiyle delesyon tarandı. Pozitif saptanan hastalar için klinik izlem protokolü oluşturuldu.

Bulgular: Hastaların %7.6 (n=5) delesyon saptandı. Dördü konotrunkal kalp anomalileri grubundandı. Tüm hastalarda kalp anomalisine ek olarak sendromun diğer klinik bulgularından en az biri mevcuttu. Fasiyal dismorfizm ve gelişme geriliği en sık saptanan klinik sorunlardı. Kognitif yetersizlik, beslenme sorunları, hipokalsemi, psikiyatrik sorunlar, bağışıklık sisteminde değişiklikler saptanan diğer klinik bulgulardı. Ebeveyn değerlendirmesi sonucunda bir annede de delesyon pozitifliği saptandı.

Sonuç: Tüm seçilmiş konotrunkal kalp anomalisi olan olgularda ve sendromun diğer anomalilerinin saptandığı kalp anomalili olgularda 22q11.2 delesyonun taranması gerektiği düşünülmektedir. Delesyon pozitifliği bulunan tüm olgular diğer anomaliler açısından da değerlendirilmeli ve genetik danışma sağlanmalıdır.

Anahtar kelimeler: 22q11.2 delesyonu, konotrunkal anomaliler, Floresan in situ hibridizasyon

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Introduction

Congenital heart defects (CHD) are the most common major birth defects in humans [1]. Identifiable genetic etiologies are reported to be as high as 40% in syndromic CHD, including single gene disorders and chromosomal anomalies [1,2]. Conotruncal cardiac defects (CCD) and aortic arch anomalies, the outflow tract anomalies of the heart, may be presented as isolated cases, but usually accompany dysmorphic syndromes. Di George Syndrome, deletion of 22q11.2, is one of the most common human micro deletion syndromes and a typical example for this entity [3,4]. Genes located at the 22q11.2 locus lead to the embryonic development of the third and fourth pharyngeal arches yielding to the formation of cardiac outflow tract, great arteries, parathyroid glands, thymus, mid-face features derived from these neural crest originated arches. In spite of advanced diagnostic techniques such as multiplex ligation-dependent probe amplification (MLPA) and chromosomal microarray studies Fluorescence in Situ Hybridization (FISH) is still the most common and practical method used for screening this micro deletion syndrome [5,6].

Chromosome 22q11.2 deletion is presented in a wide spectrum of clinical features. Its frequency is 2.8-5% congenital heart defects [7,8]. In conotruncal defects this rate is reported as 10-19.4% in different studies [7,9]. Double outlet right ventricle (DORV), Tetralogy of Fallot (TOF), aortico-pulmonary window, truncus arteriosus (TA), abnormal conotruncal cushion defect, transposition of great arteries (TGA), branchial arch defects, interrupted aortic arch (IAA), double arcus aorta, sub-arterial ventricular septum defect (VSD) and right arcus aorta, the outflow tract malformations of the heart, are classified as "conotruncal cardiac defects" by Clark in 1986 [10]. A wide spectrum of clinical findings other than congenital heart defects, such as dysmorphic faces (ocular hypertelorism, bulbous nasal tip, lowset and posteriorly rotated ears), cleft palate, hypocalcaemia, T-cell mediated immune deficiency and velopharyngeal insufficiency accompany the 22q11.2 deletion syndrome. Learning difficulties, speech and feeding problems, psychiatric disorders are also common. Musculoskeletal and renal defects are less recognized clinical findings [4]. The deletion occurs as a de novo in 93% of the patients, but can be inherited in autosomal dominant fashion, that's why genetic counselling is very important for the affected families [4]. There is no genotype and phenotype correlation within the clinical features even among the same family members [4].

This study was designed to determine the frequency of 22q11.2 deletion in a sample of patients, having conotruncal cardiac defects or other congenital cardiac defects with the extra cardiac features of 22q11.2 deletion. We also aimed to form a follow up guide for evaluating the patients and their families to provide genetic counselling.

Materials and methods

This study was performed in Pediatric Genetics and Pediatric Cardiology departments of a tertiary health care center. A total of 66 patients having congenital cardiac defects were evaluated. Patients with conotruncal anomalies were the major patient group. Conotruncal cardiac defects were determined as TOF, TA, DORV, TGA, aortic arch anomalies, based on Clark's pathogenetic classification [10]. Patients with non- conotruncal cardiac anomalies enrolled to the study if they have at least one of the following features of 22q11.2 deletion syndrome: facial dysmorphism, laryngomalaise, cleft palate, hypocalcaemia, esophageal atresia, tracheoesophagial fistula, immune deficiency and neurodevelopmental delay. Two dimensional echocardiography was performed by two experienced pediatric cardiologists to define the cardiac anatomy of each patient.

For routine cytogenetic analysis, 1-3 ml of peripheral venous blood sample with sterile injectors containing 0.2 ml heparin was obtained from each patient. Conventional chromosomal analyses were performed in the Pediatric Genetic Diagnostic Laboratories to obtain chromosome plaques. Slide preparation of chromosome plaques were prepared by Giemsa-Trypsine method (GTG-taping) for the evaluation under light microscope and karyotype images were evaluated with the Olympus BX51 microscope-linked 3.9 version Applied Imaging Automatic Image Analysis System.

Slide preparations for FISH study were carried out by standard methods and hybridization fluid with probe mixture were prepared for each case. After spreading the mixture onto the slides in dark room conditions; a cover slip over the probe was fixed with protective glue for denaturation and hybridization. Fluorescence signals were examined with an x100 immersion lens on an Olympus BX 51 fluorescence microscope, which had a filter compatible with fluorescein isothiocyanate (FITC), tetramethyl rhodamine isothiocyanate (TRITC) and 4, 6-Diamidino-2-phenylindole dihydrochloride hydrate (DAPI). Signals related to DGCR were screened in at least 100 interphase nuclei and 10 metaphase chromosomes. In our kit, the TUPLE1 signals were red with Cy3 and the control region (ARSA-Arylsulfatase 22q13.3) was green with FITC. By using a 'double / triple band pass' filter in the fluorescence microscope we expected to observe two red-two green signals in the interphase nuclei and metaphases in non-deleted cases, whereas two green-one red signals in deleted ones [11,12]. FISH analyses were carried out with locus specific 'Di George/VCFS (TUPLE1, ARSA control) double color region specific probe' [Vysis Inc., Downers Grove, IL.]

For the patients having 22q11.2 deletion, physical examination, imagining and laboratory studies were performed again to find out other accompanying clinical features of the syndrome with regard to Tobias' suggestions [13]: Hypocalcaemia, thyroid dysfunctions, blood cell counts, velopharyngeal insufficiency, neuromotor and neuropsychiatric development delay, immunity problems, renal abnormalities (Table 1).

Finally parents of the affected patients underwent karyotype and FISH analyses. Genetic consultation was also performed for the future. Informed consent was obtained from the parents of all participants.

Table 1: The follow up protocol of the deletion positive patients

Evaluation topics	Parameters	Methods
Endocrinological Examination	Serum calcium, parathormone levels Free T4, TSH levels	Venous blood sample
Otorhinolaryngological Evaluation	Morphology	Routine examinations
	Audition	Auditory and autoaucustic tests
	Velopharyngeal insufficiency	Video nasal pharyngoscopy
Developmental and psychiatric evaluation		Child psychiatry consultation
Hematologic and Immunologic Evaluation	Leukocyte count Absolute lymphocyte count Thrombocytes Mean platelet volume	Complete blood count
	Leukocyte distribution Platelet morphology	Peripheral smears
	Thrombocyte function	Bleeding time by Ivy method
	Lymphocyte subgroups (CD3, CD4, CD8, CD56, CD19)	Flow cytometer
	Immunoglobulin levels	IgA, Ig G, IgM, IgE
Visceral anomalies		Abdominal ultrasonography
Genetic counselling	Karyotype analysis FISH analyses	Medical Genetics consultation

Results

Totally 66 patients aged between 4/365 days and 16. 5 years; 38 (57.6%) male and 28 (42.5%) females enrolled to the study. Fifty-six (84.8%) patients had a conotruncal anomaly and 10 (15.2%) had a non-conotruncal congenital cardiac anomaly. The features of both patient groups are summarized in Table 2 and Table 3.

Table 2: Conotruncal cardiac defects of the patients

Defect Type	n	%
Tetralogy of Fallot	34	51.5
Double outlet right ventricle	4	6
Transposition of Great Arteries	9	13.5
Truncus arteriosus	4	6
Aorticopulmonary window	1	1.5
Double arcus aorta	2	3
Atrioventricular septal defect with aortic arch anomaly	2	3

Table 3: Clinical features of non-conotruncal cardiac defect patients

	ASD	VSD	Pulmonary stenosis	Hypoplastic left heart	ASD +VSD
Facial dysmorphism	2			1	
Laryngomalacia	1				
Neurodevelopmental delay			1		
Cleft palate		1			
EA+TEF		1			
Facial dysmorpism+ EA+TEF+ Hypocalcemia		1			1
Facial dysmorpism+ Neurodevelopmental delay+Hypocalcemia			1		

ASD: Atrial septal defect, VSD: Ventricular septal defect, EA: Esophageal atresia, TEF: Tracheoesophageal fistula

All patients underwent karyotype analysis and except one patient all results were normal (Figure 1 and Figure 2).

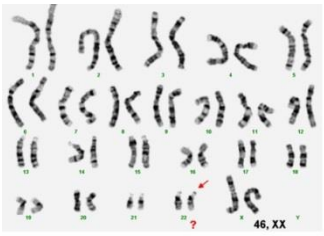

Figure 1: The karyotype of patient 3 (46,XX; Normal)

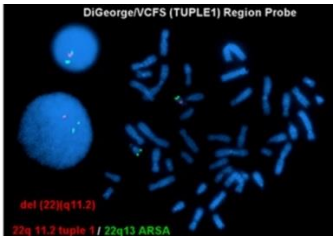

Figure 2: FISH analyses of patient 3, TUPLE1 signals were marked red with Cy3 (Cyanine dye) whereas the control region (ARSA-Arylsulfatase 22q13.3) was marked green with Fluorescein isothiocyanate (FITC). The observation of two red and two green signals was expected in interphase nuclei and metaphases in patients without deletion at the Fluorescence microscope by using a 'double/triple band pass' filter whereas the aim was to observe two green and one red signal in patients with deletion.

One of the CCD group patients had an unbalanced translocation with the karyotype 45, XY, der (7) t (7:22) (p22; q11.2),-22 (Figure 3 and Figure 4).

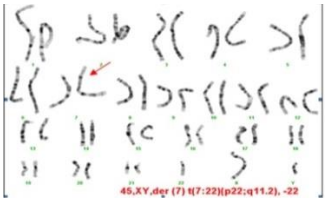

Figure 3: The karyotype of patient 4; unbalanced translocation of Chromosome 7 and Chromosome 22 resulting with the deletion of 22q11.2 region

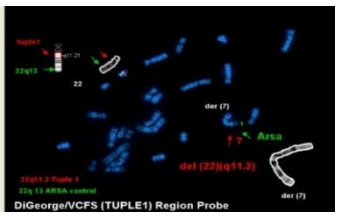

Figure 4: The FISH application of patient 4

22q11.2 deletion was detected by applying FISH method to all patients and five were found to have the deletion (7.6%). Four of the patients with deletion were from the CCD group, 3 with TOF and one with TA. All of these deletion positive patients had at least one accompanying clinical feature of 22q11.2 deletion syndrome. One patient with deletion was from the non- conotruncal cardiac defect group (10%). She had perimembranous VSD, atrial septum defect (ASD), hypocalcaemia, esophagus atresia – tracheaoesophagial fistula and facial dysmorphism.

Clinical findings other than cardiac defects of the deletion positive patients were evaluated prospectively (Table 4).

Table 4: The clinical features of 22q11.2 deletion syndrome patients

	Age Gender	Cardiac defect	Extracardiac problems	Family history
Patient 1	7/12 months Male	TOF	-Facial dysmorphism -Mildly decreased PTH with normocalcemia -Decreased CD4/CD8 without lymphopenia -Motor retardation (Denver test)	Mother, with facial dysmorphism and nasophonia, 46,XX; del 22q11.2(+)
Patient 2	3/12 months Female	TOF	-Facial dysmorphism -Hypocalcemia -Growth retardation -Reverse peristaltism in esophagus -Exitus before further evaluation because of pneumonia	None
Patient 3	6 years Female	TA	-Facial dysmorphism -Growth retardation -Neurodevelopmental delay -Selective mutism -Gastroesophageal reflux -Relative increase in CD 56; Mild increase in CD4/ CD8, no lymphopenia -Anorexia	None
Patient 4	4/365 days Female	VSD +ASD	-Facial dysmorphism -Prematurity (32 weeks), -Esophageal atresia, trachea-esophageal fistula -Hypoparathyroidism with hypocalcemia - Increase in CD 56	None
Patient 5	5/365 days Male	Tetralogy of Fallot	-Facial dysmorphism -Growth retardation -Karyotype:(45,XY, der(7)t(7:22)(p22;q11.2?),-22.;unbalanced translocation -Exitus before further evaluation	None

We weren't able to check all features in every patient although we had planned according to our follow up protocol because of survival problems. All patients had facial dysmorphism, feeding problems. Two presented hypocalcaemia. None had cleft palate or abnormal audition. One patient had communication problems and slight cognitive disability, diagnosed as 'selective mutism'. Platelet counts were within normal ranges. Thyroid functions (free T4 and TSH) in all patients were within normal ranges. Three patients could be tested for cellular immunity with CD markers. None had lymphopenia; but natural killer cell expression was increased in two patients. Immune globulin (Ig) levels could be detected in three patients and the results were compatible with age (references for laboratory evaluations [14,15]).

Family examinations of the five patients were revealed and one mother had the deletion positive (20%). She had mild

facial dysmorphism and nasophonia. The other four patients were assumed to have deletions de novo. All cases and their families were guided to the Department of Medical Genetics for genetic counselling.

Discussion

In this study the frequency 22q11.2 deletion in conotruncal and non-conotruncal cardiac defects was tested via FISH in 66 children and the frequency of the deletion was detected as 7.6% (n=5). Neither of the deletion positive patients had isolated cardiac defect, but at least one extracardiac feature of the syndrome.

FISH is still the most common method used for screening syndromes having common pathogenesis which emerges due to the loss of genetic material in the 11th region of the longer arm of the 22nd chromosome with famous names: DiGeorge Syndrome, Velocardiofacial Syndrome, Shprintzen Syndrome, Facial Syndrome with Conotruncal Cardiac Anomaly and 'CATCH 22' [4,16]. The genetic material loss by deletion and haploinsufficiency increase the variety of clinical findings and cause different phenotypes in generations within the same family [4,17]. A mother or father with no clinical signs or slight facial dysmorphism and mild velopharyngeal insufficiency, as it is the case in this study, may give birth to a baby with a severe cardiac defect [18]. In 93% of the cases, the deletion emerges 'de novo' or may be inherited in autosomal dominant manner in 6-25% of the patients [4]. In this study, compatible with the literature, one patient (20%) had maternal-originated deletion [18]. On this basis, detailed genetic counselling must be provided to the family and prenatal diagnosis possibilities must be explained well.

Seventy-five percent of the patients with 22q11.2 deletion have cardiac anomalies; most of these defects are conotruncal defects or aortic arch anomalies [19]. Among these, TOF and IAA are the most frequent ones (27-62.3%; 14-53%, respectively). Transposition of great arteries is rare [19,20]. Non-conotruncal structural cardiac anomalies are also reported, deletions may be involved in 5% of all newborns with cardiac defects [21,22]. The rate is higher in syndromic cases and patients with conotruncal cardiac anomaly. In patients having conotruncal anomalies, the frequency of deletion was reported as 2.8-4.2% [7,23]. In this study group all deletion positive patients had cardiac anomaly (7.6%; n=5). The number of patients with deletion was few, but distribution of cardiac defects was similar to the literature data, three of five had TOF, one TA, one VSD+ASD. Deletion was detected in three (8.8%) of 34 TOF patients one of four TA cases (25%). As one of the limitations of this study, the overall number of deletion positive patients was lower when compared with the literature. One reason for this could be that the number of patients with truncus arteriosus and interrupted aortic arch, which often accompany 22q11.2 deletion syndrome, was relatively low or none in this study.

Typical facial outlook is one of the prominent features of the syndrome. Upward-sloped eyebrows; short palpebral fissures; small, less convoluted, low set, posteriorly rotated ears, bulbous nose and nasal root, hypoplastic nasal wings, small mouth, micrognathia, flattening in facial mid- line structures, malar hypoplasia are characteristic findings; nevertheless they become obvious within years [5,24-26]. The findings may vary according to race and ethnicity [7]. In this study, all patients with deletion had the characteristic facial outlook of the syndrome. This situation once again emphasizes the importance of inspection in clinical evaluation.

Forty-nine (60%) of 22q11.2 the deletion positive patients display parathyroid dysfunction and temporary hypocalcaemia during infancy [27]. These patients have a tendency to arrhythmias due to cardiac anomalies that's why monitorization of serum calcium levels is recommended. Also, mineral density of the bones should be followed and early osteoporosis should be prevented. Hypothyroidism is another reported endocrinological problem [19]. In this study, hypocalcaemia was detected in two patients during neonatal period and early infancy. Thyroid functions were within normal ranges in all patients.

Eighty percent of the patients with 22q11.2 deletion display immune deficiency at varying levels [28]. T-cell count and antigenic markers must be evaluated. In this study group, no critical lymphopenia was detected and CD3 cell counts were within normal ranges with mild variations in CD4/ CD8 ratio. Early diagnosis of this problem is important because of vaccination schedule. Live vaccines are contraindicated in cellular immunity deficiencies and must be postponed until the T cell count and functions are improved [29]. Relative increase in CD56 (natural killer cells) was observed in two patients. T cell dysfunction with cardiac defects causes severe infections and necessity of intensive care unit hospitalization yielding to high healthcare costs [30]. All patients in this study experienced severe infections and hospitalized. Deletion can also cause variations in humoral immunity and tendency to severe infections may increase because of decreased antibody response [5]. Since low Ig A levels are closely related with transfusion reactions, caution is required for these patients as they are at high risk of blood and blood products exposure for various reasons. Ig levels of just three patients could be tested in this study and results were normal, compatible with age.

Palatal anomalies are frequent in patients with 22q11 deletion. Bifid uvula could be an important finding for sub-mucosal cleft palate, which can be observed by detailed physical examination [31]. Eighty percent of patients with cleft palate have velopharyngeal insufficiency. This situation, which is presented by nasophonia, articulation defects, poor feeding and nasal regurgitation, may be overlooked until the individuals begin to speak. In these cases, speech is delayed for various reasons; the problem can be diagnosed early by nasal pharyngeal endoscopy, video fluoroscopy or functional magnetic resonance imaging (MRI) so that speech therapies can begin earlier [31]. Since adenoid hypoplasia would increase velopharyngeal insufficiency, it is recommended that adenoidectomy should be avoided for these patients [5]. No palatal anomalies were detected in this study group. Also, due to patient incompatibility, only one patient could be evaluated for velopharyngeal insufficiency and pharyngeal functions were found normal with video nasal endoscopy. A study from Iran showed that 3.97% of patients with palatal problems had 22q11.2 deletion [32].

Deletion 22q11 patients may have thrombocyte dysfunction mimicking Bernard Soulier Syndrome. Since serious

bleeding may occur during surgical and invasive practices, assessment of these patients before such processes is recommended [33]. No critical thrombocytopenia, mean platelet volume (MPV) anomaly and thrombocyte dysfunction with Ivy method was observed in this group. A study in the literature suggests that the examination of 22q11 deletion is useful for those individuals who have both congenital cardiac disorders and MPV > 10fl [34].

Though it does not attract much attention, poor feeding is one of the most frequent problems. Functional problems of the gastrointestinal system such as motility disorders and anorexia are common. Due to the nasopharyngeal regurgitation caused by velopharyngeal insufficiency, the swallowing of liquid food is more difficult [5]. Poor feeding was a common problem for the affected patients of this group.

Many patients with 22q11 deletion syndrome have slight to moderate cognitive disability and require special education. The incidence of autism, attention deficit-hyperactivity syndrome, anxiety disorders, depression and obsessive-compulsive disorders are frequent [35]. Moreover, 20-30% of these patients may apply with schizophrenia or schizoid-affective disorders in adulthood [36,37]. This situation, which is often overlooked by families, causes socialization problems in these children. Supporting the child with psychiatric counselling and family education may be the solution of many problems. Similarly, one patient in this study group displayed shyness and affection disorder as well as slight cognitive disability. She could communicate only with her mother and was diagnosed with 'selective mutism' by Child Psychiatry.

In this study all cases with deletion had extracardiac clinical features of the syndrome. Particularly facial dysmorphism was accompanied by cardiac anomalies. Similarly, Khositseth et al. [24] reported that cardiac anomalies are accompanied by other clinical findings in cases with deletion. Frequency of 22q11.2 deletion in children with conotruncal heart defects was reported as 30% in another study from Turkey and the explanation of this high rate was that all patients had other dysmorphic findings of the syndrome [25]. On this basis, in routine clinical practice, examination of 22q11 deletion in all rare conotruncal anomalies such as interrupted aortic arch and truncus arteriosus is offered but for other congenital heart defects it is suggested when one of the accompanying features of the syndrome is detected.

The age of diagnose for the syndrome varies from center to center. In one study, 210 patients with 22q11 deletion were examined retrospectively and the age of diagnose for 34% of them was before one year old. Cardiac defects are the most remarkable findings for diagnosis [38]. In this study, cardiac anomalies were the key feature of the evaluation and all patients except one six year old girl were diagnosed during the neonatal period or early infancy.

In differential diagnosis, 4q deletion, unbalanced translocations or genetic arrangements related to the 22nd chromosome, 5q11.2 deletion and 10p deletion must be considered. Maternal diabetes mellitus, fetal exposure to alcohol and retinoic acid derivatives, maternal folate insufficiency may also result in similar clinic syndromes [39,40].

One of the limitations of this study is the non-exploration of the precise size of the deletion, which could have helped in establishing a genotype-to-phenotype correlation better. This study was designed for screening the deletion. Also all patients could not be evaluated for every clinical feature of the syndrome because of short survival. There is no gained new knowledge about this well-known syndrome with this study, but all clinical features are reviewed for general practitioners to provide a systematic follow up protocol for their patients and organize the treatment in a better way.

In conclusion clinical presentation of deletion 22q11 syndrome can be extremely variable. Various organ systems may be involved. For early intervention and management, early recognition of the deletion is important. The immediate performance of 22q11.2 screening for selective conotruncal anomalies (TA, IAA) via FISH analysis in addition to chromosome analysis is recommended as the severity of the cardiac anomaly shortens survive of the patients. It is clear that the rate of detection of the deletion increases if the test is applied to patients who have at least one other sign of the syndrome in addition to conotruncal anomaly. However this may cause some isolated cases with deletion to be under diagnosed, but selection is necessary for cost effectiveness. Concerning non-conotruncal cardiac anomalies, application of the test seems to be appropriate if at least two accompanying signs of the syndrome (facial dysmorphism, cleft palate, velopharyngeal insufficiency, hypocalcemia, cellular immune deficiency, speech and behavioral disorders) are present. The evaluation of the patients' parents is essential to determine the hereditary cases and for genetic counselling to provide further benefits with the chance of prenatal diagnosis.

Clinical follow-up of the 22q11.2 deletion positive patients must be carried out by a multidisciplinary teamwork [13, 39] (Table 1). Risks such as hypocalcaemia, immunity, vascular anomalies and platelet dysfunctions must be taken into consideration before surgical operations. Required modifications in diet and vaccinations must be in consideration. As some patients have tendency to severe, recurrent infections due to immune insufficiency, the treatment of infections should not be delayed. Besides; motor, behavior, speech developmental processes must be closely followed. For those patients who have speech problems and behavioral disorders, psychiatric counselling must be requested and families must be supported in this regard. An improved life quality for the patients and their families would be the success of a well-organized teamwork.

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