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Clinical and immunophenotypic characteristics of patients with chromosome 22q11.2 deletion syndrome: a single institution's experience

Kromozom 22q11.2 delesyon sendromlu hastaların klinik ve immünofenotipik özellikleri: tek merkez deneyimi

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Abstract

Aim: The aim of this study was to identify the clinical and immunologic features of patients with 22q11.2 deletion syndrome who were followed up in our clinic. Thus, it is aimed to identify the syndrome early, choose the right treatment options according to humoral and cellular immunologic analysis, and enlighten how to follow up these kinds of patients with immunodeficiencies.

Material and Methods: We retrospectively collected data by reviewing the files of 11 patients with 22q11.2 deletion syndrome who were followed up in our clinic between January 2003 and January 2015. The diagnoses were based on the patients' clinical, genetic, and immunologic features. Demographic features, family history, initial symptoms on admission, physical findings, and results of immunologic studies of the patients. Age of diagnosis, treatment options, and clinical follow-up were evaluated.

Results: The patients' diagnosis age ranged from 1-11 months and the most common symptoms of admission were cardiac murmur and atypical facial appearance, which were detected during a routine physical examination. All patients had cardiac anomalies, and four patients had a history of cardiovascular surgery. Eight patients (72.7%) had a history of severe infection; recurrent lower respiratory tract infections were reported in six patients (54.5%), pulmonary tuberculosis in one patient (9.1%), and moniliasis resistant to treatment was detected in one patient. None of the patients required intravenous immunoglobulin replacement therapy, and antibiotic prophylaxis was administered to two patients with lymphopenia.

Conclusion: 22q11.2 deletion syndrome is a multi-systemic disorder that should be evaluated by a multidisciplinary team. It should be kept in mind for patients with neonatal hypocalcemic tetany or recurrent infections or atypical facial appearance with cardiac anomalies. Early diagnosis should lead to immunologic analysis and enable the choice of treatment. Preventive measures against infection is recommended for the patients with incomplete immunodeficiency, and thymus transplantation is recommended for patients with complete immunodeficiency.

Keywords: 22q11.2 deletion syndrome, cellular immunity, DiGeorge syndrome

Öz

Amaç: Bu çalışmada kliniğimizde 22q11.2 delesyon sendromu tanısı ile izlenmekte olan hastaların klinik ve immünolojik niteliklerinin tanımlanması amaçlanmıştır. Böylece hastalığın erken tanınmasına yardımcı olmak, humoral ve hücresel immünolojik verilere göre tedavi seçeneklerine yönlendirmek ve bu immün yetersizlik hastalarının nasıl izleneceğine ışık tutmak hedeflenmiştir.

Gereç ve Yöntemler: Kliniğimizde, Ocak 2003-Ocak 2015 tarihleri arasında 22q11.2 delesyon sendromu tanısı ile izlenmekte olan 11 olgunun dosya verileri geriye dönük olarak incelendi. Hastaların tanısı; klinik, genetik ve immünolojik niteliklere göre konuldu. Çalışmaya alınan tüm hastaların demografik nitelikleri, aile öyküsü, başvuru yakınmaları, fizik bakı bulguları, immünolojik inceleme sonuçları, tanı yaşı, tedavi seçeneği ile klinik izlemleri irdelendi.

Bulgular: Hastaların tanı yaşı 1-11 ay arasında değişmekte olup, en sık başvuru yakınması fizik bakı sırasında farkedilen atipik yüz görünümü ve kalpte duyulan üfürüm idi. Tüm hastaların kalbinde anomali bulunur iken, dört hastada kardiyovasküler cerrahi girişim öyküsü vardı. Sekiz hastada (%72,7) ciddi enfeksiyon geçirme öyküsü olup; altı hastada (%54,5) sık tekrarlayan alt solunum yolu enfeksiyonu, bir hastada (%9,1) akciğer tüberkülozu ve bir hastada (%9,1) inatçı moniliazis saptandı. Lenfopenik olan iki hastaya (%18,2) antibiyotik profilaksisi uygulanırken, hiçbir hastada intravenöz immünglobulin replasman tedavisi gereksinimi olmadı.

Çıkarımlar: Kromozom 22q11.2 delesyon sendromu, çoklu organ tutulumu nedeniyle birçok uzmanlık dalıyla birlikte izlenmelidir. Yenidoğan döneminde hipokalsemik tetani geçiren, kalp anomalisine eşlik eden atipik yüz görünümü olan ve yineleyen enfeksiyon öyküsü olan hastalarda mutlaka akla getirilmelidir. Erken tanı ile hastaların immün sistem incelemesinin yapılması; kısmi eksiklik durumunda enfeksiyonlardan koruyucu önlemler alınmasını, tam hücresel immün bozukluk olması durumunda ise timus nakli yapılmasına olanak sağlayacaktır.

Anahtar sözcükler: 22q11.2 delesyon sendromu, DiGeorge sendromu, hücresel immünite

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Introduction

22q11.2 deletion, which occurs as a result of deletion of the long arm of the 22nd chromosome, is one of the most common microdeletion syndromes observed in the community. Its prevalence is known to be 1/4000. However, recent studies reported that the 22q11.2 deletion was more frequent in the population (1, 2). Although de novo mutations are found in a great percentage of patients, autosomal dominant inheritance is reported in approximately 20% (3, 4).

Although chromosome 22q11.2 deletion syndrome manifests with immunodeficiency secondary to thymus hypoplasia/aplasia, cardiovascular anomaly, characteristic facial appearance, growth retardation, and hypocalcemia secondary to hypoparathyroidism, it has a considerably wide spectrum of clinical variability (3). The presence of a large variety of phenotypic characteristics makes the diagnosis difficult in some patients and the diagnosis is made in advanced periods of life, especially if underlying congenital heart disease is absent (5). Conotruncal cardiac anomaly is found in approximately 75% of patients diagnosed as having chromosome 2q11.2 deletion and these are the most important anomalies that influence mortality (3). The most common conotruncal anomalies include Fallot tetralogy, truncus arteriosus, and interrupted arcus aorta (5). Besides these anomalies, almost all cardiac anomalies may accompany 22q11.2 deletion syndrome. A reduction in the number of T cells (incomplete immune deficiency) is reported in 75–80% of patients as a result of examination of the humoral and cellular immune system (6). A mild reduction in the number of T cells causes frequent infections, especially viral infections, and a predisposition to bacterial infections in these patients (7, 8). The number of T cells may be very low in 0.1% of patients (complete immunodeficiency or severe immunodeficiency); these patients are considered a pediatric emergencies and thymus transplantation is recommended (6).

The aim of this study was to describe the typical clinical findings of patients who were followed up with a diagnosis of chromosome 22q11.2 deletion syndrome, and to evaluate these patients in the immunologic aspect. Thus, it was aimed to help early diagnosis and follow-up for this disease, which is under recognized by physicians.

Material and Methods

The data of patients who were followed up with a diagnosis of chromosome 22q11.2 deletion syndrome between January 2003 and January 2015 in Istanbul University Cerrahpaşa Medical Faculty, Division of Infectious Diseases, Clinical Immunology and Allergy, were investigated retrospectively by examining patient files and electronic registry systems. The patients' demographic information, family histories, symptoms at presentation, laboratory findings (immunologic, biochemical, endocrinologic) and ages at the time of diagnosis were recorded. Accompanying diseases and problems and treatments administered during clinical follow-up were recorded.

For a complete blood count, blood samples were obtained and placed in EDTA (ethylendiamine tetraacetic acid) tubes and examined using a Beckman Coulter LH780 device. The total white blood cell count, lymphocyte count, and neutrophil count were determined by making comparisons with age-appropriate standard values. The numbers of CD3+ T lymhocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, CD19+ B lymphocytes, and CD16/56+ NK cells were determined simultaneously using a Beckton Dickinson Facs Calibur flow cytometer device in Cerrahpaşa Medical Faculty, Department of Pediatrics, Pediatric Immunology Laboratory using monoclonal antibodies. Immunoglobulin (Ig) G, A, and M levels were measured using nephelometry with a ROCHE COBAS 702 device, and IgE concentrations were measured using the immunoCAP method. Genetic diagnosis was confirmed by demonstrating chromosome 22q11.2 deletion with fluorescence in situ hybridization (FISH) in all patients.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained for the study from the local ethics committee of our hospital (February 2018 - Decision number: 1790). Written informed consent was obtained from the parents of all patients.

Statistical analysis

The SPSS program (Version 20.0, IBM Company, SPSS Inc.) was used for statistical analysis. Numerical data are expressed as mean±standard deviation and categorical data are expressed as frequency (n) and percentage (%).

Results

The median age of the 11 patients included in the study was 8 years (range, 3.5 months – 13 years; mean 7.16±4.73 years). Six patients were male and five were female. The median age at the time of diagnosis was found as 3 (range, 1–11; mean 4.77±3.68) months. The parents of two patients had consanguineous marriage. None of the patients had a familial history of immunodeficiency. The symptoms at the time of presentation included cardiac murmur in four patients, atypical facial apperance in three patients, hypocalcemic tetany in two patients, pneu-

Table 1. Demographic characteristics and cardiac involvements of the patients

Patient number	Sex, age	Age at the time of diagnosis, symptoms at presentation	Cardiac anomalies	History of cardiovascular surgery
1	Male, 5 years 6 months	11 months, cardiac murmur	VSD, ASD, AC, PH	Yes
2	Female, 13 years	2.5 months, hypocalcemic convulsion	RAA, PDA, PH	No
3	Male, 5 years 6 months	3 months, cardiac murmur	VSD, ASD, TOF, RAA, AC, PA, PDA, PH	Yes
4	Female, 6 months	4 months, cardiac murmur	VSD	No
5	Female, 2 years	8 months, pneumonia	VSD	No
6	Female, 11 years	2 months, hypocalcemic convulsion	ASD, PH	No
7	Male, 10 years	11 months, cardiac murmur	VSD, ASD, TA, PDA, PH	Yes
8	Male, 10 years	6 months, atypical facial appearance	VSD, ASD, TOF, RAA, PDA	Yes
9	Male, 3.5 months	1 month, atypical facial appearance	VSD, ASD, PA, PDA	No
10	Male, 13 years	2 months, atypical facial appearance	ASD	No
11	Female, 8 years	2 months, sepsis	VSD, ASD	No

AC: Coarctation of aorta; ASD: Atrial septal defect; PA: Pulmonary atresia; PDA: Patent ductus arteriosus; PH: Pulmonary hypertension; RAA: Right arcus aorta; TA: Truncus arteriosus; TOF: Fallot tetralogy; VSD: Ventricular septal defect

monia in one patient, and sepsis in one patient. Cardiac anomaly and chromosome 22q11.2 deletion were found in all patients. Cardiovascular surgery was performed in four patients (Table 1).

Eight patients had had severe infection. Recurrent lower respiratory infection was found in six patients, pulmonary tuberculosis was found in one patient, and refractory moniliasis was found in one patient.

Growth and development was evaluated with height and weight percentile curves. The height was found to be below the 3rd percentile (p) in five patients, 3–10 p in two patients, 10–25 p in three patients, and 25–50 p in one patient. The body weight was found to be below 3p in five patients, 3–10 p in three patients, 10–25 p in one patient, 25–50 p in one patient, and 97 p in one patient.

At least one of the following anomalies was present in the facial appearance of the patients: long hook nose, short palpebral fissure, long face, small chin, low-set ears, and a broader distance between the eyes. Eight patients were receiving special education with a diagnosis of mental / motor retardation. Three patients had a diagnosis of hyperactivity, and one patient had a diagnosis of autism. Five patients had comorbidities (epilepsy in three patients, obesity in one patient, and right dysplastic kidney in one patient).

When endocrinologic assessments were made, it was observed that the parathormone (PTH) concentration was low in three patients. The serum calcium concentration was low at the time of diagnosis in two patients. One patient had a normal serum calcium concentration, though his PTH concentration was low (PTH 4.02 pg/mL, Ca 9.9 mg/dL); this patient was considered to have partial hypoparathyroidism. Growth hormone deficiency was found in one patient and growth hormone replacement treatment was initiated. The Pediatric Endocrinology Department initiated follow-up and levothyroxine treatment in three patients because of hypothyroidism.

The median value was found to be 10,300 (range, 4600–18,700) /mm^3 for the white blood cell count, 4700 (range: 1100–9400) /mm^3 for the absolute lymphocyte count, and 155,000 (range, 15,000–799,000) /mm^3 the for platelet count. The platelet count was found to be below 150,000/mm^3 in five (45.4%) patients. When the lymphocyte subgroups were examined, it was found that the median value was 2278 (range, 602–6670) /mm^3 for the number of CD3+ T lymphocytes, 1130 (range, 198–3535) /mm^3 for the number of CD4+ T lymphocytes, and 547 (range, 108–1555) /mm^3 for the number of CD8+ T lymphocytes (Table 2). In two patients who were found to have a lower absolute lymphocyte count by age (1100/mm^3 and 1500/mm^3, respectively), the number of CD3+ T lymphocytes was found as 602/mm^3 and 870/mm^3, and the number of CD4+ T lymphocytes was found as 198/mm^3 and 495/mm^3, respectively.

Trimethoprim-sulfametoxazole prophylaxis was initiated because of recurrent lower respiratory infection in two patients who were lymphopenic. Intravenous immunoglobulin replacement treatment was not recommended to any patients who had normal immunoglobulin levels

Table 2. Laboratory findings of the patients

	Mean	Standard deviation	Median	Minimum	Maximum
PTH (pg/mL)	23.81	9.10	24.80	4.02	40.30
Ca (mg/dL)	9.30	1.54	9.80	5.20	10.90
P (mg/dL)	5.05	0.76	4.80	4.20	6.40
25-hydroxy vitamin D (ng/mL)	23.88	9.44	20.00	13.70	40.00
WBC (cells/mm^3)	10,400	3860.05	10,300.00	4600.00	18,700.00
Lymphocyte count (cells/mm^3)	4994.09	2596.85	4700.00	1100.00	9400.00
Neutrophil count (celss/mm^3)	4294.09	2441.29	3200.00	2000.00	8800.00
Hemoglobin value (g/dL)	11.24	1.31	11.50	9.50	13.60
Platelet count (mm^3)	244,363.6	208,525.9	155,000	15,000	799,000
Eosinophil count (cells/mm^3)	254.55	143.97	300.00	100.00	500.00
CD3+ T lymphocyte (%)	47.73	11.61	45.00	30.00	67.00
CD3+ T lymphocyte (cells/mm^3)	2 377.27	1 636.23	2 278.00	602.00	6 670.00
CD4+ T lymphocyte (%)	52.91	18.54	59.00	22.00	76.00
CD4+ T lymphocyte (cells/mm^3)	1 311.36	985.79	1 130.00	198.00	3 535.00
CD8+ T lymphocyte (%)	30.55	13.07	30.00	9.00	56.00
CD8+ T lymphocyte (cells/mm^3)	613.27	385.75	547.00	108.00	1 555.00
CD19+ B lymphocyte (%)	35.73	15.34	32.00	12.00	57.00
CD16/56+NK cells (%)	14.64	9.29	11.00	4.00	35.00
IgG (mg/dL)	947.45	363.36	1 080.00	484.00	1 430.00
IgM (mg/dL)	69.81	28.08	67.00	34.00	116.00
IgA (mg/dL)	74.93	65.68	36.70	12.00	179.00
IgE (mg/dL)	19.48	7.35	17.00	10.00	35.00

Ca: Calcium; CD: Cluster of differentiation (surface differentiation antigens); Ig: Immunoglobulin; NK: Naturel killer; P: Phosphorus; PTH: Parathormone

by age. BCG-itis developed in one of eight patients who were administered Bacillus Calmette-Guerin (BCG) vaccine. Vaccine-induced antibody response developed in three of four patients who were administered the measles-mumps-rubella (MMR) vaccine and no complications developed in any of them. The patients were followed up for a mean period of 78.6 months, no mortality occurred in any patients (Table 3).

Discussion

DiGeorge syndrome is associated with chromosome 22q11.2 deletion, arises from embrionic developmental defect of the 3rd and 4th pharyngeal arci, involves multiple systems, and has a wide phenotypic spectrum (9). Its main components include congenital heart disease, hypocalcemia, atypical facial appearance, and immunodeficiency. The patients we followed up presented with at least one of these findings. Thus, patients who present with at least one of these findings must be examined in terms of DiGeorge syndrome and other findings that may accompany.

Patients who have congenital heart disease or neonatal hypocalcemia are generally diagnosed in the first year of life (5). Dysmorphic facial appearance accompanying cardiac anomaly was found in all our patients and a history of severe infection was found in most of them. The diagnosis was made after investigations performed because of hypocalcemic convulsions in two patients and because of cardiac murmur heard on physical examinations in four patients. The diagnosis was made before the age of one year in all our patients.

In chromosome 22q11.2 deletion syndrome, deletion inheritance is observed in a small portion of patients (28%), de novo mutations are observed in many individuals who are newly diagnosed (3). Although screening in terms of deletion was not performed in the parents of our patients, clinical findings suggesting 22q11.2 deletion were not found in any patients. The most important factors influencing mortality in these patients include cardiac anomalies and the degree of immunodeficiency. Cardiovascular anomalies were reported in more than 80% of patients in many previous studies (3, 5, 10). Therefore, chromosomal

Table 3. Clinical characteristics of the patients

	n	%		n	%
Genetic			Antibody response against MMR	3	27,3
22q11.2 mutation	11	100,0	Atypical facial appearance	11	100,0
Cardiac anomaly	11	100,0	Growth		
VSD	8	72,7	Height		
ASD	8	72,7	<3 p	5	45,4
Fallot tetralogy	2	18,2	3–10 p	2	18,2
Right arcus aorta	3	27,3	10–25 p	3	27,3
Coarctation of aorta	2	18,2	25–50 p	1	9,1
Pulmonary atresia	2	18,2	Body weight		
Truncus arteriosus	1	9,1	<3 p	5	45,4
PDA	5	45,4	3–10 p	3	27,3
PH	4	36,4	10–25 p	1	9,1
Cardiovascular surgery	4	36,4	25–50 p	1	9,1
Endocrinologic			50–75 p	0	0,0
Hypoparathyroidsm	3	27,3	75–90 p	0	0,0
Hypocalcemia	2	18,2	90–97 p	1	9,1
Hypothyroidism	3	27,3	Psychiatric		
Growth hormone deficiency	1	9,1	Mental-motor retardation	8	72,7
Immunological			Hyperactivity	3	27,3
BCG vaccine	8	72,7	Autism	1	9,1
BCG'itis	1	9,1	History of severe infection	8	72,7
MMR vaccine	4	36,4	Antibiotic prophylaxis	2	18,2
Complication following MMR vaccine	0	0,0	IVIG replacement treatment	0	0,0
			Mortality	0	0,0

ASD: Atrial septal defect; BCG: Bacillus Calmette-Guerin, IVIG: Intravenous immunoglobulin; MMR: Measles-Mumps-Rubella; PDA: Patent ductus arteriosus; PH: Pulmonary hypertension; VSD: Ventricular septal defect

analysis is recommended in children who are found to have conotruncal heart anomalies and anomalies related to the aortic arch (Fallot tetralogy, truncus arteriosus, interrupted aortic arch, aortic arch anomalies) (5, 11). Park et al. (11) found cardiovascular anomalies in 85% of patients with DiGeorge syndrome (Fallot tetralogy in more than half) and isolated ventricular septal defect (VSD) in 20%. All our patients had cardiovascular anomalies. Fallot tetralogy was found in two patients and isolated VSD was found in two patients. Cardiovascular surgical intervention was performed in four patients.

The picture characterized by absence of thymus and marked T cell lymphopenia is defined as 'complete DiGeorge syndrome,' and the picture accompanied by milder immunodeficiency is defined as 'partial DiGeorge syndrome,' which is observed in many patients (12). A slight reduction in the number of T cells is observed in most patients, whereas severe immunodeficiency related to complete deficiency of T cells is observed in a very small portion of the patients (<1%). These patients must be followed up by immunology departments. A naive T cell count (CD4/CD45-RA) of <50/mm^3 constitutes an indication for thymus transplantation (6). The number of T cells is lower in children of all age groups who have 22q11.2 deletion syndrome compared with healthy children (13). Patients with a total T cell (CD3+ T lymphocyte) count of 800–2000/mm^3 mostly have normal serum immunoglobulin concentrations and a normal T cell proliferation response in the first years of life (6).

Thymus hypoplasia has a low level of impact on humoral immunity. The serum IgG and IgM concentrations are mostly normal (12, 13). Although immunoglobulin A deficiency and specific antibody response deficiency are found in a very small number of patients, they are found with a higher rate in this patient group compared with the general population (13). In the study conducted by Patel et al., (14) hypogammaglobulinemia was found in 6% of patients with DiGeorge syndrome after the age of 3 years

and immunoglobulin replacement treatment was administered to 3% of the patients. Similarly, Cancirini et al. (5) found that 3% of patients with hypogammaglobulinemia received intravenous immunoglobulin treatment. The serum IgA concentration was found to be borderline low in only one of our patients and immunoglobulin replacement treatment was not needed in any of our patients.

Sepsis has been reported in 7% of patients with DiGeorge syndrome and recurrent respiratory tract infection has been reported in approximately 50% (5). Cancirini et al. (5) reported that 17% of patients used broad-spectrum antibiotic for prophylaxis for infection control. Although the T cell count is found to be relatively lower in these patients in all age groups compared with healthy children, an association of this finding with the increased frequency of infections and autoimmunity risk could not be demonstrated (13). Although only two of our patients were lymphopenic, eight patients had a history of severe infection. Increased frequency of infections can be explained with cardiovascular anomalies, structural disorders of the face, humoral or cellular immune system changes, and atopic structure.

Primary immunization is recommended in all patients because of the risk for increased infections. However, the decision of administering live viral vaccines should be made according to the patient's specific findings including thymus aplasia and T cell count. Administration of measles, mumps and rubella (MMR) and chicken pox vaccines has been reported to be safe in patients with a slight reduction in the T cell count (15, 16). Measles, mumps and rubella vaccine was not administered because of lymphopenia in 2 of 9 patients who were aged above one year. The MMR vaccine was administered to four patients and complications did not develop in any of these patients. Antibody responses were found to be sufficient in three patients and insufficient in one patient.

It has been reported that most patients with B22q11.2 deletion who have been administered BCG vaccine tolerate the vaccine well and BCG-itis or extensive disease develops in a minority of patients (16). BCG vaccine was administered to eight of our patients and BCG-itis developed in only one patient. In this patient, the total, helper and suppressor T cell counts were found to be low (CD3+ T lymphocyte 1.200/mm^3, CD4+ T lymphocyte 264/mm^3, CD8+ T lymphocyte 108/mm^3), and serum immunoglobulin concentrationss were found to be normal by age.

In chromosome 22q11.2 deletion syndrome, endocrinopathies (hypoparathyroidism, hypothyroidism and short stature) are commonly observed (17). Hypocalcemia may accompany in some patients with hypoparathyroidism. Ryan et al. (3) found the frequency of hypocalcemia to be 60% in a patient group with 22q11.2 deletion and reported that hypocalcemic convulsions accompanied in more than half of these patients. The prevalence of hypocalcemia has been found to range between 30% and 48% in different studies (5, 18). Two (18.2%) of our patients presented with hypocalcemic convulsions and hypocalcemia secondary to hypoparathyroidism was found in both patients. In our center, patients followed up with a diagnosis of 22q11.2 deletion syndrome are interrogated in terms of hypocalcemia findings, and serum Ca, P, ALP, PTH concentrations are checked at regular intervals. Hypocelcemia did not develop during the clinical follow-up in our patients except for two patients. Short stature is frequently observed both structurally and because of underlying systemic disease. Growth retardation is observed with a high rate in patients with congenital heart disease (3). In five of our patients, the height or body weight was found to be below the 3rd percentile. Thyroid dysfunction is also a common endocrinopathy in these patients (9). Three of our patients were receiving hormone replacement treatment with a diagnosis of hypothyroidism. In the literature, growth hormone deficiency has been reported with a rate of 4% in this patient group (19). One of our patients was receiving hormone replacement treatment with a diagnosis of growth hormone deficiency.

Although genitourinary anomalies are observed in 36% of the patients in the literature, we found dysplastic kidney in only one patient in our study (3). Therefore, patients diagnosed as having 22q11 deletion syndrome should routinely be screened using urinary tract ultrasonography in terms of structural kidney anomalies.

Dysmorphic clinical findings and laboratory test results compatible with the phenotypic and genotypic characteristics of 22q11.2 deletion syndrome were found in all our patients. The primary limitation of our study was the low number of patients.

Chromosome 22q11.2 deletion syndrome is a disease involving multiple systems that occurs with an important frequency in the population and should be followed up in association with many specialities. In the presence of findings suggesting this syndrome, chromosomal analysis should be requested for diagnosis, and screening in terms of involvement of other systems should be performed. Considering that patients with this syndrome are sometimes diagnosed in the late period with findings including frequent infections, neuromotor developmental retardation, and speech disorder, it is important to raise the awareness of general practitioners and pediatricians in terms of these phenotypic characteristics (5).

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from our hospital's local ethics committee (February 2018, Decision number: 1790).

Informed Consent: Written consent was obtained from the parents of all patients.

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References

1. Grati FR, Molina Gomes D, Ferreira JC, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. Prenat Diagn 2015; 35: 801–9.
2. Goodship J, Cross I, LiLing J, Wren C. A population study of chromosome 22q11 deletions in infancy. Arch Dis Child 1998; 79: 348–51.
3. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 1997; 34: 798–804.
4. Swillen A, Devriendt K, Vantrappen G, et al. Familial deletions of chromosome 22q11: the Leuven experience. Am J Med Genet 1998; 80: 531–2.
5. Cancrini C, Puliafito P, Digilio MC, et al. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. J Pediatr 2014; 164: 1475–80.
6. Morsheimer M, Brown Whitehorn TF, Heimall J, Sullivan KE. The immune deficiency of chromosome 22q11.2 deletion syndrome. Am J Med Genet A 2017; 173: 2366–72.
7. Staple L, Andrews T, McDonald-McGinn D, Zackai E, Sullivan KE. Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease. Pediatr Allergy Immunol 2005; 16: 226–30.
8. Perez E, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes). Curr Opin Pediatr 2002; 14: 678–83.
9. Brown JJ, Datta V, Browning MJ, Swift PG. Graves' disease in DiGeorge syndrome: patient report with a review of endocrine autoimmunity associated with 22q11.2 deletion. J Pediatr Endocrinol Metab 2004; 17: 1575–9.
10. McDonald-McGinn DM, Kirschner R, Goldmuntz E, et al. The Philadelphia story: the 22q11.2 deletion: report on 250 patients. Genet Couns 1999; 10: 11–24.
11. Park IS, Ko JK, Kim YH, et al. Cardiovascular anomalies in patients with chromosome 22q11.2 deletion: a Korean multicenter study. Int J Cardiol 2007; 114: 230–5.
12. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet 2007; 370: 1443–52.
13. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE. Immunologic features of chromo-some 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pe-diatr 2001; 139: 715–23.
14. Patel K, Akhter J, Kobrynski L, et al. Immunoglobulin deficiencies: the B-lymphocyte side of DiGeorge Syndrome. J Pediatr. 2012 Nov;161(5):950-3.
15. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE. Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 2003; 112: e325.
16. Suksawat Y, Sathienkijkanchai A, Veskitkul J, et al. Resolution of Primary Immune Defect in 22q11.2 DeletionSyndrome. J Clin Immunol 2017; 37: 375–82.
17. Weinzimer SA. Endocrine aspects of the 22q11.2 deletion syndrome. Genet Med 2001; 3: 19–22.
18. Taylor SC, Morris G, Wilson D, Davies SJ, Gregory JW. Hypoparathyroidism and 22q11 deletion syndrome. Arch Dis Child 2003; 88: 520–2.
19. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. Am J Med Genet A 2005; 138: 307–13.