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Original investigation

How Much do we Know About the Findings of 22q11.2 Deletion Syndrome?: A Single-Centre Study with 11-Year Follow-Up

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ABSTRACT

Purpose: 22q11.2 deletion syndrome is a contiguous gene deletion syndrome with multisystem involvement characterized by cardiac defects, immunodeficiency and hypocalcemia. Variable expression and a wide range of clinical findings make it difficult for clinicians to decide on the test.

Methods: Evaluation was made of the clinical findings of patients who underwent the FISH test for 22q11.2 deletion syndrome between 2006 and 2017.

Results: Of the 180 patients, 152 (84.45%) had cardiac defects, 5 (2.78%) had immune defects, 132 (73.4%) had dysmorphic findings and 52 (28.89%) had growth / developmental delay. Ten patients had 22q11.2 deletion syndrome (5.56%) and 9 of these had cardiac defects. Hypocalcemia was present in 5 (50%) patients and only one patient had immunodeficiency.

Conclusion: In this study, the accuracy of the indication was evaluated retrospectively based on the clinical findings of patients who underwent FISH analysis for 22q11.2 deletion syndrome. In cases with congenital cardiac defects, although 22q11.2 deletion syndrome is one of the possible diagnoses of the clinician, a detailed examination of the defect type before testing will increase the diagnosis rate. It should be kept in mind that this syndrome should be considered in the presence of major findings such as immunodeficiency or hypocalcemia.

Keywords: 22q11.2 deletion syndrome, congenital cardiac defect, immunodeficiency, hypocalcemia

INTRODUCTION

22q11.2 deletion syndrome (22q11.2DS) was first described by Digeorge in 1968 (1). It is the most common microdeletion syndrome, with a frequency of approximately 1/4000 but it is thought to be more frequent due to the variable expression. (2–4). Although the clinical findings of 22q11.2DS are highly variable, approximately 77% of the patients have an immune defect, 74% have cardiac defects, and 50% have hypoparathyroidism-induced hypocalcemia. In addition, approximately 69% of the patients have palatal defects and 70–90% have learning difficulties (2).

The proximal 22q region is rich in LCRs (Low Copy Repeats). The deletion occurs as a result of nonhomologous allelic recombination between LCRs. Typical LCR A-D deletion of 3Mb size is seen in 85% and atypical deletions (LCR A-B, B-D or C-D) are seen in 15% of cases (2). In the LCR A-D region, there are 46 protein coding genes, including *TBX1* (T-BOX 1) (5). Major findings in 22q11.2 deletion syndrome are thought to be the result of defects in the *TBX1* gene. This gene is a transcription factor gene that is thought to be effective in neural crest migration through growth factors (6). In the presence of a typical deletion, Fluorescence in situ Hybridization (FISH) analysis is sufficient for diagnosis. However, if there is an atypical nested deletion, it is usually necessary to use other methods such as Multiplex Ligation-dependent Probe Amplification (MLPA) or Chromosomal Microarray (CMA) (2).

The findings of this syndrome may vary from mild to severe defects, with an extremely wide variety of findings, such as hypernasal speech, psychiatric symptoms or severe heart defects (6–8). Therefore, in order for this syndrome to be one of the initial diagnoses, patients should be evaluated by experienced clinicians. The aim of this study was to retrospectively assess the accuracy of the diagnostic indication in patients who presented with 22q11.2DS.

METHODS

Study Subjects

A retrospective review was made of all patients who presented with 22q11.2DS at our clinic from January 2006 to July 2017. The patients included in the study were those who were referred to us because of congenital cardiac defects (especially conotruncal defects), palatal abnormalities (particularly velopharyngeal insufficiency), hypocalcemia, immunodeficiency, learning difficulties, characteristic facial features and who underwent FISH analysis for suspected 22q11.2DS. Exclusion criteria were the presence of chromosomal abnormalities or another diagnosis explaining the clinical findings. Sociodemographic data, the type of specimen (peripheral blood, cord blood or amniotic fluid), consanguinity, examination findings and laboratory data were evaluated. This study was approved by the Ethics Committee of Dokuz Eylul University.

Fluorescence in situ Hybridization

After peripheral blood cell cultures and fixation were prepared in accordance with the standard cytogenetic procedure, FISH analysis was performed according to the manufacturer's protocol (Vysis, Abbott Molecular, Illinois, USA). The slides containing the cell sample were incubated in 2xSSC (saline-sodium citrate) buffer and then dehydrated by serial ethanol dilution (70%, 85% and 100% respectively). After waiting for 5 min at 37°C on the hotplate, 10 mcl of probe for each sample was dropped onto the slide sample and a coverslip was attached. The slide was allowed to stand for 2 minutes at 75°C on the hotplate for denaturation, then kept overnight at 37°C in a humid and light-proof environment. After removal of the coverslip, post hybridization washing was performed using SSC and Tween-20. Following the application of 10 mcl DAPI to each sample, the coverslip was added and the slide was examined with a fluorescence microscope.

RESULTS

The sociodemographic and clinical data of the patients are given in Table 1. A total of 180 patients underwent FISH analysis for 22q11.2DS. There were 25 (13.8%) prenatal samples taken at mean 20.96±3.44 (range, 16–30) gestational weeks. Of the 145 (93%) samples from children in the postnatal group, only 35 (22.5%) were older than 1 year of age. Deletion was detected in 10 of these patients (5.56%), 2 of which were prenatal patients diagnosed with amniocentesis material. One of the positive results was from fibroblast samples. The consanguinity rate was quite high.

Patients with clinical 22q11.2DS

Cardiac Anomalies

No heart defects were detected in 27 patients. In 10 patients (5.88%) tetralogy of Fallot (TOF) was determined and 6 (60%) of these were isolated. In 1 patient there was seen to be truncus arteriosus in addition to tricuspid insufficiency, left pulmonary artery stenosis, persistent left superior vena cava and Eisenmenger syndrome. Left ventricular hypertrophy, primary pulmonary HT, atrial septal defect (ASD) and dextrocardia were also present in a patient with interrupted aortic arch. Right aortic arch was found in 2 patients. Ventricular septal defect (VSD) was determined in 50 (29.4%) of the cases, and 10 (20%) of these were isolated. Patent ductus arteriosus (PDA) was determined in 34 (20%) patients. Other than the cardiac defects described above, 39 patients (22.9%) had other congenital heart defects such as ASD, total anomalous pulmonary venous connection (TAPVC), transposition of the great arteries (TGA) or hypoplastic left heart syndrome. Pulmonary artery anomalies were present in 22 (13%) patients.

Other Findings

Hypoparathyroidism was present in 8 (4.7%) patients, 2 of whom had normal calcium levels. In 4 (2.35%) patients, an immune defect was detected, in 15 (8.82%), a palatal defect of which 13 were cleft lip/palate. Ear abnormalities and/or hearing deficits were determined in 41 (21.8%) patients, and visual disturbances and/or eye abnormalities, most commonly strabismus, in 27 (15.9%). The other most common congenital anomalies in patients were skeletal system and genitourinary system anomalies. The most common CNS abnormalities were ventriculomegaly. Behavioral problems were seen in 3 patients and these were pervasive developmental disorder, self-injury and attention deficit hyperactivity disorder.

Patients *with* 22q11.2DS

The findings of the 22q11.2 deleted patients are shown in Table 2. Only one patient with deletion had no cardiac defect. Three patients had TOF and one patient had truncus arteriosus (pulmonary atresia, hemitruncus and atrial isomerism).

Table 1. Sociodemographic and clinical findings of the patients applied for 22q11.2DS

	Patients with 22q11.2DS			Patients with clinical 22q11.2DS		
Patients	**Prenatal (n=2)**	**Postnatal (n=8)**	**Total (n=10)**	**Prenatal (n=23)**	**Postnatal (n=147)**	**Total (n=170)**
Specimen type						
Peripheral blood		7	7		146	146
Amniotic fluid	2		2	10		10
Cord blood				13		13
Fibroblast bx		1	1		1	1
Age (mean value)	17.5 ± 2.12 (16-19) Gestational weeks	3.77 ± 3.47 (0.084-10) Age		21.26 ± 3.4 (16-30) Gestational weeks	3.26 ± 8.25 (0.084-41) Age	
Gender n (F/M)	--	3 (37.5%) / 5 (62.5%)	--	--	62 (42.1%) / 85 (57.9%)	--
Presence of consanguinity	0 (0%)	1 (12.5)	1 (10%)	4 (17.3%)	35 (23.8%)	39 (22.9%)

Table 2. Clinical findings of the 22q11.2DS patients

Patient number	Sample type	Growth / Developmental delay	Dysmorphic facial findings	Hearing defects	Visual disturbances and/or eye abnormalities	Cardiac defects	Other dysmorphic findings	PTH levels	Clacium levels	immunodeficiency
1	PB	Yes	Hypertelorism, epicantus	Yes	NI	No	NI	Low	Low	NI
2	PB	NI	NI	NI	NI	Truncus arteriosus, pulmonary atresia, atrial isomerism	NI	NI	NI	NI
3	PB	Yes	Flat and wide ear helixes, bilateral epiblefaron, small eyes, depressed nasal bridge	NI	NI	TOF, VSD	Timus agenesis	NI	Low	NI
4	PB	Yes	Bulbous nasal tip	Yes	No	PDA	No	Normal	Low	No
5	Amniotic fluid	-	-	-	-	Dextrocardia, single ventricul	Cleft palate, holoprosencephaly	-	NI	-
6	Fibroblast bx	NI	Low ear sets, depressed nasal bridge	No	No	TOF, right aortic arch, PDA	No	Low	Low	No
7	PB	Yes	Micrognathia, hemangioma on the left of the midline in the palate, prominent nasal bridge, broad nasal root	No	No	TOF, right aortic arch, AVSD, PS	NI	NI	NI	NI
8	Amniotic fluid	-	-	-	-	DORV	NI	-	-	-
9	PB	Yes	Sparse hair, depressed nasal bridge, antevert nostrils	NI	NI	VSD	Axial hypotonia, esophagus atresia	NI	Low	NI
10	PB	Yes	triangle face, prominent ears	No	No	VSD, PDA	Cryptorchidism	NI	Normal	Yes

PB: Peripheral blood; **NI:** Not indicated; **TOF:** Tetralogy of Fallot; **VSD:** Ventricular septal defect; **PDA:** Patent ductus arteriosus; **AVSD:** Atrioventricular septal defect; **PS:** Pulmonary stenosis; **DORV:** Double outlet right ventricle

Of the patients with deletion, 6 (60%) had growth/developmental delay, 5 (50%) had hypocalcemia, 2 (20%) had hypoparathyroidism, 1 (10%) had immune defect, 2 (20%) had palatal defect and 2 (20%) had hearing deficits.

DISCUSSION

Cardiac defects are the main cause of mortality in children with 22q11.2DS (5). After Down's syndrome, it is the second most common chromosomal reason for congenital cardiac defects (9). Most cardiac defects are conotruncal anomalies such as tetralogy of Fallot, truncus arteriosus or aortic arch anomalies (10). Ventricular septal defect is the most common finding in patients admitted for 22q11.2DS. Atrial septal defect and PDA, which are atypical findings, appear to be the second most common reason for admission due to cardiac defect. These non-typical findings are seen in patients with deletions but are very rare. There were seen to be few patients with conotruncal cardiac defects in the current study compared to the literature. In addition, the abundance of atypical cardiac findings suggests that the clinician who requested the FISH test was inexperienced about this syndrome.

Although inadequate in terms of typical findings, it has been observed that this syndrome is taken into account sufficiently in patients with heart defects. When the patients undergoing FISH analysis were examined, it can be seen that there are very few patients with immune defects, suggesting that immunologists are not sufficiently aware of 22q11.2DS. As other clinical findings and complications are emphasized more in literature it can be said that immunological findings remain in the background (11). Thymus aplasia or the absence of T cells makes the diagnosis of 22q11.2 deletion syndrome easier. Especially in the presence of a low T cell count, increased number of infections, atopy and autoimmune diseases (due to T cell defect) (11), this syndrome should be considered among the preliminary diagnoses.

Another common finding for 22q11.2DS is the presence of hypocalcemia. Clinical findings of hypocalcemia are not observed in most cases. Hypocalcemia can be transient, repetitive and permanent. It is thought that hypoparathyroidism can be prevented by treatment of hypocalcemia (12). Therefore, it will be in the best interest of patients to be aware of this not uncommon finding. The fact that hypocalcemia was not found in the clinical 22q11.2DS patients can be interpreted as this finding does not lead to initial consideration of 22q11.2DS by physicians. Similarly,

the low incidence of palatal defect in patients with clinical 22q11.2DS suggests a low awareness of this finding.

The diagnosis rate in patients with clinical 22q11.2DS ranges from 4% to 78.2% (13). In addition to a wide range of findings, variable expression appears to be the most important cause of this wide diagnostic range. Another reason is the methodological differences in the studies. For example, patients with deletions <40 kb cannot be diagnosed by FISH testing (2). With advancements in technology and current advances in genetics, smaller deletions or duplications have become detectable by methods such as CMA. In a study by Bahamat et al., 2 of 30 (6.67%) clinical 22q11.2DS patients were diagnosed by FISH analysis, whereas an additional 6 patients were diagnosed when aCGH (Array Comparative Genomic Hybridization) was performed (14). In another study involving 347 patients, the diagnosis rate by FISH and MLPA analysis was 28.2% (13). In the same study, 132 patients underwent CMA and 5 had atypical deletions. It was also shown in that study that the diagnostic rate increased 3.82-fold when the test was performed based on the diagnostic criteria proposed by Monteiro et al (13, 15). In the current study, the diagnosis rate was 5.56%, which was similar to rates in literature. The absence of any selection criteria for the test in the current study may explain the low diagnosis rate. Another limitation of this study was that patients with normal FISH analysis for 22q11.2 deletion could not be examined by analysis such as MLPA and CMA. It is possible to say that there will be an increase in the number of patients diagnosed after these tests.

22q11.2 deletion syndrome requires a multidisciplinary approach involving a large number of departments due to the wide range of clinical findings. Since it is also a common syndrome, physicians should be aware of this syndrome and have enough knowledge about this syndrome for it to be among the initial diagnoses, thus increasing the number of diagnosed patients.

Compliance with Ethical Standards: This study was approved by the ethics committee of Dokuz Eylul University. (2018/27-19)

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