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Clinical variability of chromosome 22q11.2 deletion syndrome

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Abstract

22q11.2 deletion syndrome (22q11.2 DS) is a disorder that has multiple symptoms and affects various organs and systems. Despite the great variability of clinical manifestations, common 22q11.2 DS includes congenital heart defect, immunodeficiency, characteristic facial features, palatal defects, developmental and/or learning disabilities, and hypocalcaemia. We present the cases of three patients with 22q11.2 DS that we have observed. Heart defects were revealed in all cases, and tetralogy of Fallot in one of them. Immune system disorders in these cases were highly variable and did not correlate with aplasia or hypoplasia of the thymus. Cleft palate was diagnosed only in one case. Characteristic facial features were presented in all cases but they were not significant and varied from subtle to mild. Developmental disability was presented by motor delays in two cases. Hypocalcaemia was revealed in one patient, and seizures were absent. Only one case completely fit CATCH-22 syndrome (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcaemia caused by22q11.2 deletion). The other cases had three out of the five main features, with some other, less significant signs also presented. In some cases, even just a few signs should be the reason for further examination to exclude 22q11.2 deletion syndrome. Currently, immunological disorders are not a significant determinant in the diagnosis of this syndrome, and timely correction of heart defects can reduce the number of recurrent respiratory infections. A multidisciplinary approach to the management of these patients and providing timely, complex medical care will prevent serious complications.

Key words*: children, 22q11.2 deletion syndrome, clinical variability.*

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Introduction

DiGeorge syndrome, velocardiofacial syndrome (Sphrintzen syndrome), conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, and Cayler cardiofacial syndrome are different terms of the syndromes that have in common the same genetic cause – microdeletion on chromosome 22 at band 22q11.2 [1, 2]. So today the common term for all these syndromes is 22q11.2 deletion syndrome (22q11.2 DS). Its estimated prevalence is 1 in 4000 live births and it is the most common microdeletion syndrome [3].

22q11.2 DS is a highly variable syndrome involving various organs and systems. A genetically confirmed defect allows definitive diagnosis of 22q11.2 DS, but when a diagnosis relies only on clinical features the term DiGeorge syndrome can be used [2].

Despite the great variability of clinical manifestations, common 22q11.2 DS includes congenital heart defect, immunodeficiency, characteristic facial features, palatal defects, developmental and/or learning disabilities, and hypocalcaemia [3-5]. Renal anomalies, psychiatric disorders, feeding and swallowing problems, hearing loss, laryngotracheoesophageal anomalies, and growth retardation are less common symptoms. In some cases, autoimmune disorders, centre nervous system anomalies, skeletal abnormalities, ophthalmologic abnormalities, enamel hypoplasia, and malignancies may occur [6].

Characteristic facial features of varying degree of expression occur in all patients [7]. They commonly include long face, hypertelorism, retrognathia or micrognathia, narrow palpebral fissures, prominent nose with large tip and hypoplastic nares, small mouth with everted upper lip, small teeth, low-set dysmorphic ears, short philtrum, and asymmetrical crying face [3, 6-8].

Immunodeficiency in children with 22q11.2 DS is associated with hypoplasia or aplasia of the thymus, which is responsible for making T cells [2, 3, 9], so these children often suffer from recurrent viral and fungal infections. Depending on thymus hypoplasia or aplasia, DiGeorge syndrome is classified as partial or complete [9, 10].

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Developmental delay and/or learning disabilities can vary from mild to severe and occur in about 90% of cases [3]; sometimes they are the main symptoms and a reason for admittance to a psychiatric department [9].

Case reports

We present the cases of three patients (two girls and one boy) with 22q11.2 deletion syndrome that we have observed over the last five years. In all cases, the diagnosis was based on clinical and laboratory evaluation and by detection of the chromosome 22q11.2 microdeletion.

Laboratory evaluation included complete blood count test with differential and quantitative measurement of immunoglobulin levels (IgG, IgM, IgA, IgE) in blood serum with enzyme immunoassay (ELISA).

Immunophenotyping of peripheral blood lymphocytes by flow cytometry involved evaluation of T cells, B cells, and NK cells.

Functional activity of immune cells (neutrophils) was evaluated by oxidative burst assay with Nitroblue Tetrazolium (NBT test).

The chromosome 22q11.2 microdeletion was verified using fluorescence in situ hybridisation (FISH) analysis. FISH analysis with TUPLE1 probes within the most commonly deleted region was done during the first year of life and in two cases during the neonatal period.

Prior written informed consent was obtained from the individual participants of the studied cases. The experimental protocol was carried out in accordance with the guidelines of the Helsinki Declaration of 1975, as revised in 2000.

Case 1

A two-year-old boy is being followed by a paediatric immunologist and other sub-specialists due to 22q11.2 deletion syndrome (DiGeorge syndrome).

He was born after a second full-term pregnancy, complicated by dysfunction of the placenta, gestational oedema, and mild polyhydramnios via spontaneous vaginal delivery, weight 3300 g, body length 51 cm, head circumference 35.0 cm. Family history was non-contributory. Prenatal ultrasound examination was performed at the 20th week of gestational age in a district hospital, but congenital heart defect was not detected due to insufficient capacity of the ultrasound equipment used for the examination.

The general state of the child after birth was moderate for neurological problems caused by birth trauma – cephalhaematoma of the occipital area and congenital malformation – incomplete closing of the soft palate. On the second day after birth a cardiac murmur was noted and congenital heart defect and DiGeorge syndrome were suspected.

In the second week of his life, the diagnosis was clarified after an ultrasound scan: congenital heart defect – double outlet right ventricle (DORV), ventricular septal defect (VSD), valvular stenosis of the pulmonary artery; congenital palatal defects – incomplete closing of the soft palate; birth trauma – intraventricular haemorrhage and cephalhaematoma of the left occipital areas.

At the age of 1.5 months, after a surgical X-ray examination of the heart and large vessels, the diagnosis of congenital heart defect was confirmed and clarified: DORV, tetralogy type, stenosis of pulmonary artery branches on the bifurcation (PS), secondary atrial septum defect (ASD II), aberrant right subclavian artery (Table 1). Palliative surgery (balloon dilatation of the stenosis) was performed. At the age of six months radical correction of the heart defect was performed.

FISH analysis was carried out at the age of 1.5 months and confirmed the diagnosis of microdeletions on the long arm of chromosome 22q11.2.

Dysmorphic features include low-set, malformed ears, shot philtrum, high arched palate, hypertelorism, and small mouth (Fig. 1). Muscular hypotonia occurred in the first year of life.

From the 7th to 12th months of life the boy was twice treated as an inpatient. The first time he was admitted to the department of surgery with a diagnosis of ulcerous-necrotic

Table 1. Clinical features of chromosome 22q11.2 deletion syndrome in the studied cases

Features	Case 1	Case 2	Case 3
Heart defect	DORV + PS + ASDII	VSD	TF
Thymic hypoplasia or aplasia	Hypoplasia	Aplasia	Aplasia
T-cell deficiency	No	Yes	Yes
Recurrent infections	Yes	Yes	No
Characteristic facial features	Yes	Subtle	Yes
Palatal defects	Yes	No	No
Developmental and/or learning disabilities	Mild	No	Mild
Hypocalcaemia	Yes	No	No
Seizures	No	No	No

Fig. 1. Dysmorphic features (low-set, malformed ears, shot philtrum, hypertelorism, small mouth) in patient No. 1

Fig. 2. Mild developmental motor delay in patient No. 1 at one year old

enterocolitis, secondary mesadenitis, erosive gastroduodenitis, and enteropathy. Median laparotomy with the exploration of abdominal cavity, mesentery lymph node biopsy, and abdominal lavage were performed. The second time the boy was admitted to the department of infectious diseases with severe course of pneumonia and obstructive syndrome.

Bacterial stool culture contained *Klebsiella*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida fungi*. Throat culture showed *Streptococcus viridans* and *Escherichia coli*.

During the first year of the child's life we noticed mild growth retardation. At the age of one year his weight was

Table 2. White blood cells and immunological details of chromosome 22q11.2 deletion syndrome in the studied cases

Parameter	Case 1	Case 2	Case 3
Cells/mm^3 (%)	6 months of age	6 months of age	8 months of age
Leukocytes	9600	6290	12 700
Neutrophils	4320 (45%)	2440 (38.8%)	4000 (31.5%)
Lymphocytes	3648 (38%)	2849 (45.3%)	6591 (51.9%)
Monocytes	672 (7%)	818 (13%)	2108 (16.6%)
CD3	2115 (58%)	1504 (52.8%)	2702 (41%)
CD4	1350 (37%)	920 (32.3%)	1252 (19%)
CD8	693 (19%)	538 (18.9%)	922 (14%)
CD19	766 (21%)	1037 (36.4%)	1055 (16%)
CD14	ND	103 (3.6%)	ND
CD3/56	ND	43 (1.5%)	ND
CD16/56	328 (9%)	279 (9.8%)	ND
CD45	ND	99.7%	ND
IgG	9.1 g/l	5.7 g/l	12.8 g/l
IgA	0.95 g/l	0.5 g/l	2.1 g/l
IgM	0.84 g/l	0.44 g/l	1.4 g/l
IgE	3.8 IU/ml	ND	ND
Functional activity	ND		ND
Spontaneous		117 opt.un.	
Induced		292 opt.un.	
Phagocytic index		2.5	

ND – not done

8300 g, body length 71 cm, and mild developmental motor delay was determined (Fig. 2).

In the second year of life the boy received outpatient treatment for onychomycosis on both hands, with a positive effect.

Laboratory investigations revealed serum ionised calcium level ranging from 0.61 to 0.94 mmol/l (normal 0.95-1.05 mmol/l), so calcium supplementation was prescribed. Immunological studies showed normal levels of T cells, B cells, and immunoglobulins (Table 2). Blood count parameters were also normal. Despite the low level of calcium, the patient had no seizures.

Case 2

A one-year-old girl was born after a second full-term pregnancy via spontaneous vaginal delivery, weighting 3200 g. The pregnancy was complicated by dysfunction of the placenta and the threat of interruption at 11 weeks. Chronic herpes infection was diagnosed in the pregnant mother. Family history was non-contributory. Congenital heart defects (membranous ventricular septal defect [VSD] and open oval window) were confirmed on the second day of life.

At the age of 1.5 months the girl was admitted to the Department of Infectious Diseases in critical condition, with severe respiratory, cardiovascular, and neurological disturbances. Bilateral pneumonia and urinary tract infection were diagnosed. Enterococcus faecalis was revealed in urine culture. At the age of 4.5 months open oval window was confirmed and subarterial ventricular septal defect and high pulmonary hypertension were diagnosed. Increased levels of Ig G herpes virus type I-II, Ig G cytomegalovirus, Ig G Epstein-Barr virus, and Ig G rubella virus were determined. CRP was also elevated.

Palliative surgery (narrowing of the pulmonary artery) was carried out at the age of five months. During the surgery, absence of thymus was revealed. The postoperative period was complicated by prolonged hyperthermia, which required long-term use of antibiotic therapy.

Immunological studies showed low levels of cytotoxic cells (CD3+, CD56+) – 1.5% (normal range 3-8%) and slightly decreased CD4+ at 32.3% (normal 33-58%) and monocytes / macrophages (CD14) – 3.6% (normal range – 6-13%). B-lymphocytes (CD19+) were slightly increased at 36.4% (normal range – 13-35%). While percentage values of CD3+, CD8+, NK-cells, and immunoglobulins were normal, the absolute values of CD3+, CD4+, CD8+, and NK cells were moderately reduced (Table 2). NBT test was normal. FISH analysis on metaphase plates using Vysis TUPLE1 (HIRA) Spectrum Orange/LSI ARSA Specrtum Green [Abbott] confirmed the chromosome 22q11.2 deletion: ish del(22)(q11.2q11.2)(TUPLE1–).

This patient had no palate abnormalities. Characteristic facial features were very subtle. Auxological parameters were normal. At the age of one year her weight was 9000 g, body length 76 cm. Developmental disabilities were absent in this period. Serum calcium level was normal and seizures were absent (Table 1).

Case 3

A six-month-old girl was born after the first full-term pregnancy via spontaneous vaginal delivery, weighting 2840 g. The pregnancy was complicated by exacerbation of herpes infection in the second month of the pregnancy. Congenital heart defect (tetralogy of Fallot [TF]) was diagnosed antenatally. Second-level examinations, such as amniocentesis and genetic analysis, were not offered to the parents during the pregnancy. Apgar scores were 7 per 1 minute and 7 per 5 minutes. The general condition of the patient after the birth was grave due to respiratory and cardiovascular disorders. Family history is not clear, but there were some neonatal period deaths and incidences of heart disease in close relatives.

Congenital heart defect – TF was confirmed in the first day of life. Nasal regurgitation was observed in the first months. There was physical development retardation. At the age of 11 months her weight was 6150 g. There was a mild motor delay. Dysmorphic findings were mild.

Laboratory findings showed normal serum ionised calcium level. The thymus was not visualised by computed tomography scanning. Immunological studies revealed low levels of CD3+ (by percentage) and CD4+ (by percentage and absolute numbers) T lymphocytes. Other subtypes of T lymphocytes (by percentage and absolute numbers) and immunoglobulins were normal (Table 2). Recurrent infections were not observed (Table 1).

At the age of three weeks FISH analysis revealed chromosome micro-deletions in 22 q11.2 locus, female karyotype: 46,XX.ish del(22)(q11.2)(HIRA-).

Vaccinations of hepatitis B and pneumococcal infections were carried out.

At the age of five months radical correction of the heart defect was performed.

Discussion

The deletion on the long arm near the central part of chromosome 22 causes 22q11.2 deletion syndrome, which leads to disruptions of organogenesis in the third and fourth pharyngeal pouches. The syndrome is associated with abnormal development of the thymus, parathyroid gland, heart, great vessels, head and neck, brain, skeleton, etc. It leads to hypocalcaemia, T-cell deficiency, and various structural defects of the heart, vessels, and soft palate [1-3].

In all the presented cases, there were complicated courses of pregnancy. In the second case the threat of interruption at 11 weeks and probably intrauterine mixed infection (herpes virus I-II, cytomegalovirus, Epstein-Barr virus, rubella virus) were observed.

Heart defects were detected in all of the cases. The frequency of congenital heart disease in children with 22q11.2 DS ranges from 75% [3] to 82% [7]. Conotruncal defects are the most common, and tetralogy of Fallot is the most frequent among them [10] – it was diagnosed in one of our cases. 10-15% of all patients with tetralogy of Fallot have chromosome 22q11.2 deletion [3]. 22q11.2 DS is the second most common cause of large congenital heart defects after Down syndrome [3].

DiGeorge syndrome was first described as a severe immunodeficiency. Now it has been reported that immunodeficiency in 22q11.2 DS can be mild to moderate [2] even in cases where the thymus is hypoplastic or absent [10, 11], and it occurs in 40 to 77% of patients [3, 10]. Only 0.5-1% of patients with 22q11.2 DS have severe immunodeficiency [3]. Usually these patients have complete DiGeorge syndrome with thymic aplasia. As the thymus is responsible for making T cells, their low number and/or impaired function may occur [7]. This can cause recurrent infections, and in some cases autoimmune diseases might develop [3]. A small number of patients with 22q11.2 DS have decreased immunoglobulin levels, and 2-3% of them require immunoglobulin replacement therapy [10, 12]. However, thymic defects leading to T-cell deficiency are not the only cause of immunodeficiency. Other structural defects, such as heart defects and cleft palate are risk factors for infections. The highest risk of recurrent infections exists in the first years of life, and after that children and adults usually do not have recurrent infections [7].

Only in the second case, which was associated with thymic aplasia, were recurrent infections and T-cell deficiency diagnosed. In the first case, recurrent infections were in the background of thymic hypoplasia, but the levels and function of T cells were normal. In contrast, in the third case, in the background of thymic aplasia, we observed reduction in T-cell lymphocytes, but infections were absent. Timely vaccination against pneumococcal infection might have helped to avoid serious infections.

Thus, disorders of the immune system in patients with 22q11.2 DS are highly variable and do not always correlate with aplasia or hypoplasia of the thymus.

Palatal anomalies are found in two thirds [3, 4] to 75% [7] of patients with 22q11.2 DS. Their spectrum is variable. Velopharyngeal insufficiency is the most common. Of the cases in this report, cleft palate was observed only in one patient.

Characteristic facial features were presented in all of our cases, and this corresponds with the literature [3, 7]. They were not significant and varied from subtle to mild.

Developmental and/or learning disability/ mental retardation are among the most common symptoms of 22q11.2 DS. Developmental delays include delays in motor, linguistic, and cognitive functions [13]. Delays of the motor function are often associated with hypotonia [7]. In two of our cases delays in motor skills were diagnosed, and in one case they were associated with hypotonia.

Besides that, the most common neurological signs in patients with 22q11.2 DS are attention deficit, hyperactivity, impulsivity, distractibility, and perseveration [3].

Monitoring and follow-up of neural development is important for all ages because speech and learning difficulties may manifest later in life. Psychiatric disorders develop in 30-60% of adults with 22q11.2 DS, including schizophrenia and other psychotic disorders (in about 20% of all cases) [3].

Hypocalcaemia is diagnosed in more than 60% of 22q11.2 DS patients [3, 10] mostly in the neonatal period. Seizures occur much less often. In our cases hypocalcaemia was revealed in one patient and seizures were absent, possibly due to calcium replacement therapy.

Follow-up of the three patients with 22q11.2 DS has demonstrated great variability of clinical manifestations and their severity.

Only the first case included all features of CATCH-22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcaemia caused by 22q11.2 deletion). The other cases had three of five main features, with other less significant signs also presented.

Recurrence in the family (autosomal dominant) of the 22q11.2 DS is detected in about 8-28% of cases [14]. A more complex phenotype is presented in the second generation. Therefore, all cases of the syndrome require genetic testing of parents. Unfortunately, in our cases genetic testing of the parents has not yet been carried out. However, in the second and third cases the parents plan to test for 22q11.2 DS before planning the next pregnancy.

Conclusions

Despite the great clinical variability of 22q11.2 deletion syndrome, there are some key features, the combination of which allows suspicion of the syndrome from the first days of life and diagnosis of it in time. Currently, immunological disorders are not a significant determinant in the diagnosis of this syndrome, and timely correction of heart defects can reduce the number of recurrent respiratory infections. In some cases, even a few signs should compel further examination to exclude 22q11.2 deletion syndrome. A multidisciplinary approach to the management of these patients, in accordance with Practical Guidelines 2011, with the involvement of appropriate specialists and subsequent timely complex medical care, will prevent serious complications. The variability of clinical manifestations requires an individual approach to each patient with 22q11.2 deletion syndrome.

The authors declare no conflict of interest.

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