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CLINICAL FEATURES OF 22q11.2 DELETION SYNDROME: A LITERATURE REVIEW AND CASE SERIES REPORTS

Tatjana Stanković[1,2], Katarina Harfman Mihajlović[2,3], Dragana Lazarević[1,2], Karin Vasić[1,2], Hristina Stamenković[1,2]

[1]University of Niš, Faculty of Medicine, Serbia

[2]Univeristiy Clinical Center Niš, Pediatric Internal Disease Clinic, Niš, Serbia

[3]Univeristy of Niš, Faculty of Medicine, doctoral studies, Niš, Serbia

The 22q11.2 deletion syndrome is the most common microdeletion syndrome. The clinical features show a broad spectrum of multisystem manifestations and include congenital heart defects, hypoparathyroidism associated with hypocalcemia, hypoplasia of the thymus and subsequent immunodeficiency, distinctive facial features, velopharyngeal insufficiency, and developmental delay or learning disabilities. Retrospective analysis of medical data was conducted and the spectrum of clinical manifestations of case series of five patients with 22q11.2 deletion syndrome is presented. A small series of patients with a 22q11.2 deletion syndrome is described, but still a sufficient number that undisputably display a recognizable spectrum of manifestations. All patients expressed elements of facial dysmorphism and signs of immune system dysfunction which ranged from lymphopenia and recurrent respiratory infections to congenital defect in T cell immunity. Almost all of reported patients had associated conotruncal congenital heart defects, and majority of cases presented with hypocalcemia and elements of motor and developmental delay. Increased awareness of multisystemic features of 22q11.2 deletion syndrome is pivotal for early recognition and early initiation of comprehensive care and treatment.

Keywords: 22q11.2 deletion syndrome, thymus, congenital defect in T cell immunity, hypocalcemia, congenital heart defects.

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KLINIČKE KARAKTERISTIKE SINDROMA DELECIJE 22q11.2: PREGLED LITERATURE I PRIKAZ SERIJE SLUČAJEVA

Tatjana Stanković[1,2], Katarina Harfman Mihajlović[2,3], Dragana Lazarević[1,2], Karin Vasić[1,2], Hristina Stamenković[1,2]

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra Pedijatrija, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za pedijatriju, Niš, Srbija

[3]Univerzitet u Nišu, Medicinski fakultet, student doktorskih studija, Niš, Srbija

Sindrom delecije 22q11.2 je najčešći mikrodelecioni sindrom. Kliničke karakteristike pokazuju širok spektar multisistemskih manifestacija, a najčešće uključuju urođene srčane mane, hipoparatireoidizam sa hipokalcemijom, hipoplaziju timusa i posledičnu imunodeficijenciju, karakteristične crte lica, velofaringealnu insuficijenciju i razvojno kašnjenje ili smetnje u učenju. Urađena je retrospektivna analiza medicinske dokumentacije i prikazan je spektar kliničkih manifestacija kod serije od pet pacijenata sa 22q11.2 delecionim sindromom. Opisana je mala serija pacijenata sa sindromom delecije 22q11.2, ali ipak dovoljan broj ispitanika koji nesporno dočarava prepoznatljiv spektar kliničkih manifestacija u ovom sindromu. Kod svih pacijenata prisutni su elementi facijalnog dismorfizma, kao i parametri disfunkcije imunog sistema koji su se manifestovali od limfopenije i rekurentnih respiratornih infekcija do urođenog T ćelijskog imunskog deficita. Skoro svi prikazani pacijenti su imali udružene urođene konotrunkalne srčane mane, a većina obolelih je ispoljila hipokalcemiju i elemente motoričkog i razvojnog kašnjenja. Povećana svest o multisistemskim karakteristikama sindroma delecije 22q11.2 je ključna za rano prepoznavanje i blagovremeno otpočinjanje sveobuhvatne nege, praćenja i lečenja obolelih.

Ključne reči: Sindrom delecije 22q11.2, timus, urođeni deficit T ćelijskog imuniteta, hipokalcemija, urođene srčane mane.

Introduction

The 22q11.2 deletion syndrome is the most common microdeletion syndrome occurring with an estimated frequency of 1:3000 to 1:4000 live births. The 22q11.2 deletion syndrome is a multisystemic disorder that includes physical, cognitive, and behavioral problems. Previously, several disorders with a specific deletion in 22q11 region have been reported in the literature, such as velocardiofacial syndrome, DiGeorge syndrome, and a group of disorders described by the acronym CATCH22 (cardiac defect, abnormal facial features, thymic hypoplasia, cleft palate, hypocalcemia) (1,2).

Chromosome 22 is an acrocentric chromosome and deletion occurs on the proximal part of long arm of one chromosome from the chromosome pair. The 22q11 region contains several low-copy-number repeat sequences and among them deletion of regions may occur. Heterozygous deletion of the 22q11.2 region in the most of patients includes the loss of region size of 2.54Mb in which there are approximately 40 genes (3). So far haploinsufficiency of the TBX1 gene (T-box transcription factor 1 gene) in this region has been linked to many of the manifestations in 22q11.2 deletion syndrome. The TBX1 gene provides instructions for synthesis of proteins which play important roles during embryonic development, including the migration of neural crest cells and formation of the pharyngeal arch and pouches (2,4).

The spectrum of clinical manifestations in the 22q11.2 deletion syndrome show multisystem involvement and significant variability in severity of their presentation (Table 1). The main phenotypic features include the presence of a congenital heart defect, hypoparathyroidism associated with hypocalcemia, hypoplasia of the thymus and an immune deficiency, distinctive facial features as well as cleft palate or velopharyngeal insufficiency. Affected

individuals may also have developmental delays, including delayed speech development or learning disabilities.(5)

Table 1. Characteristic phenotypic features in patients with 22q11.2 deletion syndrome (1-3, 6-8)

Organ system involvement	**Phenotypic Features**	**Frequency in 22q11.2 deletion**
Immune disorders	Athymia/ Thymic hypoplasia/ Ectopic thymus Impaired T-cell production and function CD4+ lymphopenia/ and lower CD3 counts Severe combined immunodeficiency Reduced natural T regulatory cells/ autoimmunity	25-75%
Endocrine disorders	Thyroid gland aplasia/ hypoplasia Parathyroid gland dysfunction Growth hormone deficiency	30-65%
Genitourinary anomalies	Renal agenesis Multicystic dysplastic kidney Hydronephrosis Absent uterus/ Hypospadias/ Cryptorchidism	6-35%
Cardiovascular anomalies	Tetralogy of Fallot Isolated aortic arch anomaly Hypoplastic left heart syndrome Valvular pulmonary stenosis Ventricular septal defect	35-85%
Palatal anomalies	Velopharyngeal insufficiency and hypotonia Cleft palate/ Submucous cleft palate/ Bifid uvula	more than 67%
Gastrointestinal disorders	Gastroesophageal reflux Esophageal atresia Hirschprung disease	about 30%

The facial dysmorphism is characterized by a constellation of several phenotypic features, however sometimes mild and not so evident. These features include an elongated face, hypertelorism, wide nasal bridge, hooded eyelids, epicanthus, long nose with a bulbous tip, small mouth and low-set, posteriorly rotated, small ears.

The 22q11.2 deletion syndrome is the most common cause of syndromic palatal anomalies and velopharyngeal dysfunction, but also one of the most frequent causes of developmental delay and congenital heart disease (2). Additionally, it is most commonly associated with conotruncal heart defects such as tetralogy of Fallot, pulmonary atresia with ventricular septal defect, truncus arteriosus and aortic arch anomalies (6).

The aim of this report was to present the spectrum of clinical manifestations of the 22q11.2 deletion syndrome in our patients.

Material and Methods

Retrospective analysis of patients diagnosed with of 22q11.2 deletion syndrome examined during regular outpatient visits to the Genetics Clinic, Clinic of Pediatrics, University Clinical Center in Nis during a one-year period was conducted. Medical data from outpatient's medical records during the year 2023 were reviewed and collected. This evaluation included only patients with a confirmed diagnosis of 22q11.2 deletion syndrome.

Data extracted from patient medical reports included demographic data, perinatal events and neonatal history, developmental milestones, presence of facial dysmorphism, presence of congenital heart defects or other congenital anomalies, signs of immune system dysfunctions, disorders of calcium metabolism and other disorders of importance. All extracted data were summarized, evaluated and presented.

Results

In this retrospective analysis 5 patients (3 boys and 2 girls) with confirmed diagnosis of 22q11.2 deletion syndrome were evaluated. The age of the patients ranged from 4 months to 11 years (Table 2).

In the majority of reported patients, a diagnosis of 22q11.2 deletion syndrome was confirmed at an early age (in 3 patients within the first 6 months of life, in 1 patient at age of 22 months). On the other hand, in one boy (patient number 5) there was a clinical suspicion from infancy, but genetic testing was done later and a characteristic microdeletion was identified. There were no identifiable significant risk factors in prenatal and perinatal periods. All patients were born at term, with appropriate birth weight and good parameters and vital signs at delivery.

The spectrum of clinical manifestations in our group of patients is presented in Table 3. All children had distinctive facial features, which in one case were discrete and mild (patient number 3). Three of five patients presented with complex congenital heart defects at birth, such as interruption of the aortic arch (patient number 1) and Tetralogy Fallot (patients 4 and 5). These patients underwent cardiac surgery. In the remaining two children, acyanotic congenital heart defects (atrial and/or ventricular septal defect) were detected. Hypocalcaemia was found in three children (patient's number 2, 3 and 5) during the early neonatal period and just in one case manifested with seizures. However, the hypocalcemia in this patient was transient and resolved following short therapy followed by gradual increase in oral dietary calcium intake.

Table 2. The main characteristics of our patients with 22q11.2 deletion syndrome

patient	gender	age at the time of examination	age at diagnosis confirmation
No.1	female	4 months	1 months
No.2	male	9 months	2 months
No.3	female	11 months	6 months
No.4	male	4.5 years	22 months
No.5	male	11 years	10.5 years

Table 3. The main clinical manifestations of our patients with 22q11.2 deletion syndrome

patient	No.1	No.2	No.3	No.4	No.5
Facial dysmorphism	typical	typical	mild	typical	typical
Congenital heart disease	interrupted aortic arch. VSD	ASD. VSD	ASD	T.Fallot	T.Fallot
Serum calcium level	-	hypocalcemia	hypocalcemia, neonatal seizure	-	hypocalcemia
disorder of immune function	defect in T-cell immunity	defect in T-cell immunity	lymphopenia	recurrent infections	recurrent infections
Motor/intellectual development	-	slight motor delay	slight motor delay	motor delay speech delay	global develop-mental delay
Other manifestations	-	-	velopharyngeal insufficiency	-	hypospadias, renal ectopia

*VSD: ventricular septal defect; ASD: atrial septal defect; T.Fallot: tetralogy of Fallot.

A broad spectrum of immune system dysfunction was registered in the children presented in this report, ranging from lymphopenia and recurrent respiratory infections to an innate defect in the T cell immune response. All patients were referred to an immunologist for the assessment of immune dysfunction and further follow-up including surveillance of vaccination. All patients except one (patient number 5) were included in the preventive respiratory syncytial virus (RSV) immunoprophylaxis.

Two out of three our patients at age below one year showed a slight delay in acquiring motor skills. On the other side, the older patients (first at the age of four and half years, and second one at the age of eleven years) showed elements of motor and speech delay or even global developmental delay that required the initiation of a development stimulation program.

Discussion

The 22q11.2 deletion syndrome manifests with broad phenotypic variability, making early diagnosis challenging. However, the diagnosis of 22q11.2 microdeletion is often suspected in the presence of congenital heart defects, palatal defects and symptomatic early hypocalcemia associated with varying facial dysmorphism (9),

In this report we present a small case series of patients with a 22q11.2 deletion syndrome, but still a sufficient number that undisputably display a recognizable spectrum of manifestations.

Almost all of our patients had a congenital heart defect, described in literature as being associated with 22q11.2 deletion syndrome, while an isolated atrial septal defect was detected only in one patient. According to literature, cardiovascular conotruncal anomalies are present in almost 80% of neonates with 22q11.2 deletion syndrome (6,10). The most common anomalies include interrupted aortic arch, tetralogy of Fallot, truncus arteriosus, and ventricular septal defects, which corresponds to the frequency and spectrum of cardiac anomalies detected in our group of patients.

Infants with 22q11.2 deletion syndrome require diagnostic evaluation regarding immunodeficiency, considering that this problem is caused by aplasia or hypoplasia of the thymus, or disorders in the number and function of thymocytes (10). Immunodeficiency, even in cases of hypoplasia or aplasia of the thymus, can be mild to moderate and occurs in 40-77%

of patients, while only 0.5-1% of patients have severe immunodeficiency (11). Recurrent infections show the highest frequency in the first years of life. After that period the risk of frequent infections decreases. Medical records of our patients showed T cell deficiency in two patients, while the other patients showed mild immune disorders, taking into account the lymphopenia and frequent respiratory infections. Although the majority of children with 22q11.2 deletion syndrome have T cell lymphopenia, immunodeficiency is highly variable and dynamic, and immune status should be determined before immunization with live vaccines (12). At same time, during first 2 years of life RSV immunoprophylaxis should be recommended, especially in the presence of congenital heart disease (13). RSV immunoprophylaxis was administered to almost all our patients to prevent serious respiratory disease, including the patient presented with atrial septal defect and coexisting velopharyngeal insufficiency.

Hypoparathyroidism with subsequent hypocalcemia was detected in approximately 60-70% of children with 22q11.2 deletion syndrome. Hypocalcemia may be manifested at any age, but is most severe during the neonatal period presenting as hypocalcemic seizures, or during periods of stress, perioperative period or acute illness. (9,12). In our group of patients, 3 out of 5 (that corresponds to 60%) exhibited hypocalcemia during the neonatal period, including the occurrence of neonatal seizures in one case. Dietary calcium intake and vitamin D supplementation should be considered in those patients and monitoring of calcium serum levels, parathyroid hormone and vitamin D is highly recommended (12).

Palatal abnormalities with velopharyngeal dysfunction can be detected in about two-thirds of children, including cleft palate and may be related to pharyngeal hypotonia, feeding and swallowing disorders, or even obstructive sleep apnea symptoms (9). The group of children

presented in this report showed a low frequency of velopharyngeal dysfunction, except in one child with consequent severe feeding problems.

Among 22q11.2 deletion syndrome patients some less frequent symptoms may appear, such as: renal abnormalities, laryngeal-tracheo-esophageal abnormalities, vertebral abnormalities, polydactyly, scoliosis, thrombocytopenia, hearing loss or microcephaly (14). In our group of patients one child presented with hypospadias and renal ectopia.

Children with 22q11.2 deletion syndrome often present with developmental, cognitive, speech-language and communication disorders (12). During adolescence behavioral abnormalities can occur as manifestations of psychiatric disorders such as anxiety and depression (14). Almost all of our patients have manifestations related to motor skills delay, or even global developmental delay with behavioral problems. Neurologic evaluation, early interventions and stimulation of development (physical, occupational and speech therapies) can optimize better neurodevelopmental achievements.

Conclusion

Increased awareness of pediatricians about the spectrum of phenotypic and multisystemic features in 22q11.2 deletion syndrome is essential for an early suspicion, recognition and detection of disease, as well as early initiation of comprehensive multidisciplinary care and treatment.

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