



Neonatal manifestation of 22q11.2 deletion syndrome – four case reports and a mini-literature review

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Abstract

A genetic disorder caused by the microdeletion of the long arm of 22th chromosome is the most common microdeletion syndrome in humans. It is estimated that 22q11.2 deletion affects one in every 1,000 foetals and one in 4,000 live births. During the neonatal period, the 22q11.2 deletion syndrome manifests itself in children in the form of dysmorphic facial features, and the results of ultrasound imaging tests reveal thymus hypoplasia, urinary tract disorders or brain impairments. The picture is completed by congenital heart diseases which indicate a high probability of the syndrome. This report describes four cases of newborns with 22q11.2 syndrome, presenting with a variety of clinical findings typical for this genetic disorder. The patients present symptoms ranging from mild to life-threatening conditions. The severity of the congenital heart defect determines the survival rate in infancy. Each needs of each patient must be tailored to his or her specific medical problems. A holistic approach, addressing medical and behavioural needs, can be very helpful.

Key words

case report, congenital heart disease, neonate, 22q11.2 deletion syndrome, thymus hypoplasia

Abbreviations

ECG – electrocardiography; ARSA – aberrant right subclavian artery; NIPT – non-invasive prenatal testing

INTRODUCTION AND OBJECTIVE

22q11.2 deletion syndrome is a genetic disorder caused by the microdeletion of the long arm of the 22nd chromosome. *De novo* deletion accounts for a vast share of cases. In some patients, the deletion is inherited according to an autosomal dominant pattern, more often in the mother's cells. In such event, the risk of the disease in subsequent children of given parents is 50% [1]. Advanced prenatal testing methods, such as ultrasonography or foetal echocardiography, allow the diagnosis of anomalies in foetals which suggest the need to expand genetic diagnostics. Foetal defects which might suggest the 22q11.2 deletion syndrome include congenital heart defects, in particular in the aorta or the pulmonary trunk areas, and thymus hypoplasia. Other symptoms are renal anomalies, central nervous system anomalies, such as cavum septi pellucidi dilatation, palatal defects and dysmorphic facial features. Additional associated signs detected prenatally include intrauterine growth restriction and polyhydramnion. Early diagnosis, preferably made prenatally or in the neonatal period, could improve outcomes, which indicates the significance of universal screening [2].

MATERIALS AND METHOD

Analysis included the neonatal period of patients born at the neonatal department in one tertiary referral level centre between 2018 – 2022. In the period of four years, 3,140 echocardiography tests were performed, and examination results showed thymus hypoplasia/aplasia in four patients diagnosed with 22q11.2 deletion syndrome. Two additional cases of thymus hypoplasia included one case of a heart defect of the hypoplastic left heart syndrome (HLHS) type, and one case of death in the initial days after birth. The two cases were not included in the analyses due to insufficient data regarding the further fate of the patient, and the lack of parents' consent to perform genetic tests and autopsy. The current analysis covered the period of postnatal adaptation, dysmorphology assessment and imaging diagnosis. Imaging tests included ultrasonography of the brain, abdominal cavity, lungs, and the mediastinum, and echocardiography. Ultrasonography was performed using the Mindray DC-70x-Insight machine. Chest x-rays were performed only in the first and second cases. Electrocardiography tests were performed with the use of the Cardio Custo Oxford 300BT/A device. Regarding the analysis of QT interval assessment, bedside ECG monitoring cardiograms were not taken into account. In laboratory tests, attention was paid to hypocalcaemia, which was defined as total serum calcium <8 mg/dL (2 mmol/L) or ionized calcium <4.4 mg/dL (1.1 mmol/L). As regards the first and second patients, written consent was given in both cases to publish their images.

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The subsequent fate of the patients covers the period of infancy and early childhood. Genetic examinations were performed outside our centre, and therefore were not subject to detailed analysis. With regard to the first and the second patients and their mothers, the parents provided the results of tests performed using the MLPA method. The third case was confirmed prenatally on the basis of the comparative genomic hybridization-female karyotype diagnostic test which revealed genome imbalance in the form of a deletion of the long arm of chromosome 22 in the region 22q11.21. The fourth patient was subject to genetic examination using the FISH method in the centre where he underwent cardiac surgery.

CASE 1

A pre-term female infant with a birth weight of 2,180 g was delivered by Cesarean section to a 24-year-old primiparous mother. Pregnancy was complicated with hypertension, and urinary tract infection. In prenatal history, centralization of circulation was detected. Prenatal ultrasound examination did not reveal any congenital malformation, but the foetus was observed toward intrauterine growth restriction in the third trimester. In the first minutes of life, she presented persistent bradycardia and single gasping. The neonate required positive pressure insufflation followed by NCPAP breathing support. The APGAR scores were 4 at 1st and 6 at 5th minute, respectively. In a clinical examination, signs of dysmorphia, single palmar creases, small ears, bulbous nasal tip, hypotonia and typical skull shape due to pelvic position of the foetus were observed (Fig. 1). Her heart rate was in the normal range and sinus rhythm on ECG with QTc 410ms. Echocardiography revealed right aortic arch and mild flow at the level of the foramen ovale. Hypoplasia of thymus was seen in X-ray and ultrasonography. Ultrasonography of the brain and abdominal cavity was in the normal range. In the genetic examination of both the girl and her mother, 22q11.2 deletion was confirmed. Examination of the mother excluded any heart defect, arrhythmia and electrolyte disturbances. According to reports, the mother did not experience any serious infections, neither in the neonatal period nor in the teenage years. In the 3-year follow-up, echocardiography was found to be stable with intact interatrial septum. The girl had sporadic infections and her neurodevelopment was in the normal range.



Figure 1. Case 1(a) Dysmorphic features, e.g. underdeveloped chin, low set ears, wide-set eyes, narrow groove in the upper lip; (b) X-ray hypoplastic thymus, (c) Hypoplastic thymus in ultrasonography; (d) single palmar crease

CASE 2

Term infant boy, the brother of Case 1, with a birth weight of 3,200 g was delivered by Cesarean section to 25-year-old mother. Pregnancy was complicated with intestinal infection in the second trimester and maternal Group B Streptococcal colonization. Prenatal ultrasound examination did not reveal any congenital malformation. Despite the parents' knowledge of the risk of 50% 22q11.2 deletion in their offspring, they did not consent to invasive or genetic testing from the mother's blood. In the first minutes of life, the boy required positive pressure insufflation, after which his respiration was stable. The APGAR scores were 6 at the 1st and 8 at 5th minute, respectively. In a clinical examination, signs of dysmorphia, hypotonia, and small ears were noted. His electrocardiogram revealed prolonged QT interval with corrected QT interval of 480 msec (normal < 470 msec in neonate). Echocardiography revealed a muscular ventricular septal defect of 3.5mm in diameter, and mild flow at the level of foramen ovale (4mm). Thymus hypoplasia was seen in X-ray and ultrasonography of the mediastinum (Fig. 2). Ultrasonography of the brain and abdominal cavity was in the normal range. In the genetic examination, as in the case of his sister (Case 1) and mother, 22q11.2 deletion was confirmed. In the 2-year follow-up, echocardiography was found to be stable with spironolactone treatment. The boy had a single episode of pneumonia, but his neurodevelopment was in the normal range.

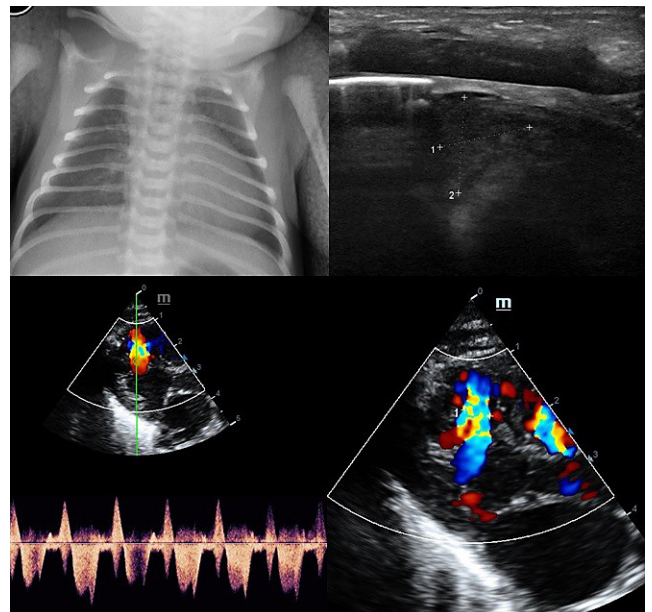


Figure 2. Case 2. Hypoplastic thymus in x-ray and ultrasonography. Echocardiography bi-directional flow at the level of ventricular septal defect in Doppler spectrum. Turbulence flow at the level of ventricular septal defect

CASE 3

Term female infant with a birth weight of 3,180 g was delivered by vaginal delivery to a 26-year-old primiparous mother. Pregnancy was complicated with polyhydramnion, urinary tract infection, and candida albicans vaginal infection. In foetal echocardiography performed in the 34th week of gestation, common arterial trunk, type I Collette and Edwards, was diagnosed. The result of foetal genetic

examination was obtained on the basis of examination of the amniotic fluid using the whole gene oligonucleotide microarray (aCGH) method. The APGAR scores were 7 at the 1st and 8 at 5th minute, respectively. In a clinical examination, signs of dysmorphia, hypotonia, and small ears were noted. Oxygen saturation was 90–95%. Her heart rate was in a normal range and sinus rhythm on ECG. Echocardiography confirmed common arterial trunk type I (Fig. 3). Ultrasonography revealed aplasia of thymus, hypoplasia of vermis and right kidney aplasia (Fig. 4). Parents were not genetically tested for the 22q11.2 deletion. The girl was transported to a paediatric cardiac surgery centre in the first week of life. The patient died at home one month after the cardiac surgery.

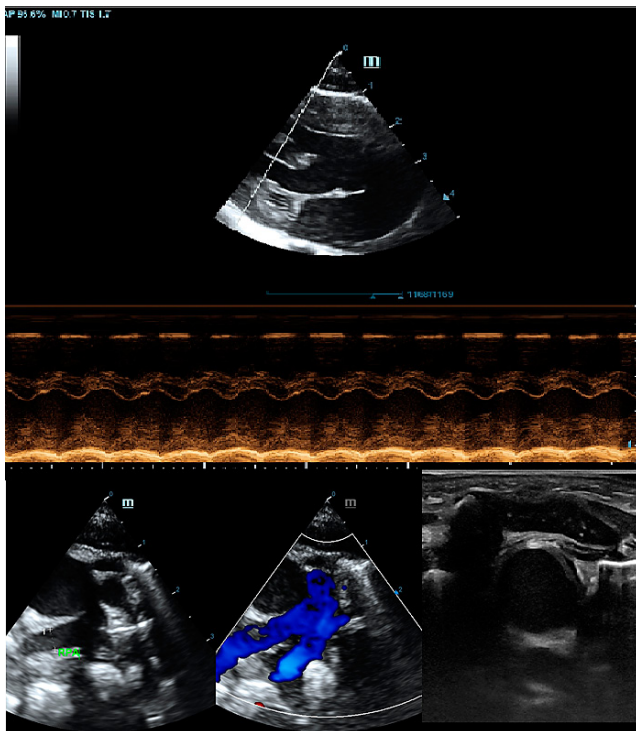


Figure 3. Case 3. Echocardiography, (a) Parasternal long-axis view and M-mode examination. Ventricular septal defect; (b) Truncus arteriosus type 1, main pulmonary artery is present and bifurcates into the left and right pulmonary arteries; (c) Upper mediastinum, thymus aplasia

CASE 4

Term boy infant with a birth weight of 3,270 g was delivered by Cesarean section to a 35-year-old primiparous mother. Pregnancy was complicated with vaginal bleeding in the third trimester. The foetus was wrapped with the umbilical cord around the neck and trunk. Prenatal ultrasound examination did not reveal any congenital malformation. In the family history, the mother's twin sister had a heart defect in the form of ventricular septal defect operated at the age of 15. The APGAR scores were 10 at the 1st and 5th minutes, respectively. In a clinical examination, signs of dysmorphia, hypotonia, and small ears were noted. In the first hours of life, coldness of the lower limbs was noticed. The screening pulse oximetry and additionally blood pressure were significantly different between the upper and lower limbs. His electrocardiogram revealed prolonged QT interval with corrected QT interval of 480–490 msec (normal < 470 msec in neonates) (Fig. 5). Echocardiography revealed aortic arch interruption type B, aberrant right subclavian artery (ARSA), stenotic aortic valve, ventricular septal defect, and bilateral flow at the level of foramen ovale (5mm) (Fig. 6). Continuous infusion of prostaglandin was used to maintain the patency of the arterial duct. Ultrasonography revealed aplasia of thymus, hypoplasia of vermis and polysplenia. In the genetic examination performed in cardiac surgery department, 22q11.2 deletion was confirmed. The patient underwent single-stage repair of the interrupted aortic arch and ventricular septal defect. The parents were not genetically tested for the 22q11.2 deletion. Information on the patient's condition covers the first six months of his life, and his further fate is unknown.

DISCUSSION

Clinical and molecular cytogenetic studies have demonstrated that *de novo* deletions of chromosome 22 occur with a high frequency, making them the most frequently occurring microdeletion syndromes found in humans. Only 10–15% of cases concern patients whose parents have a diagnosed deletion or rare structural balanced chromosomal rearrangement involving the 22q11.2 deletion region [3,4].

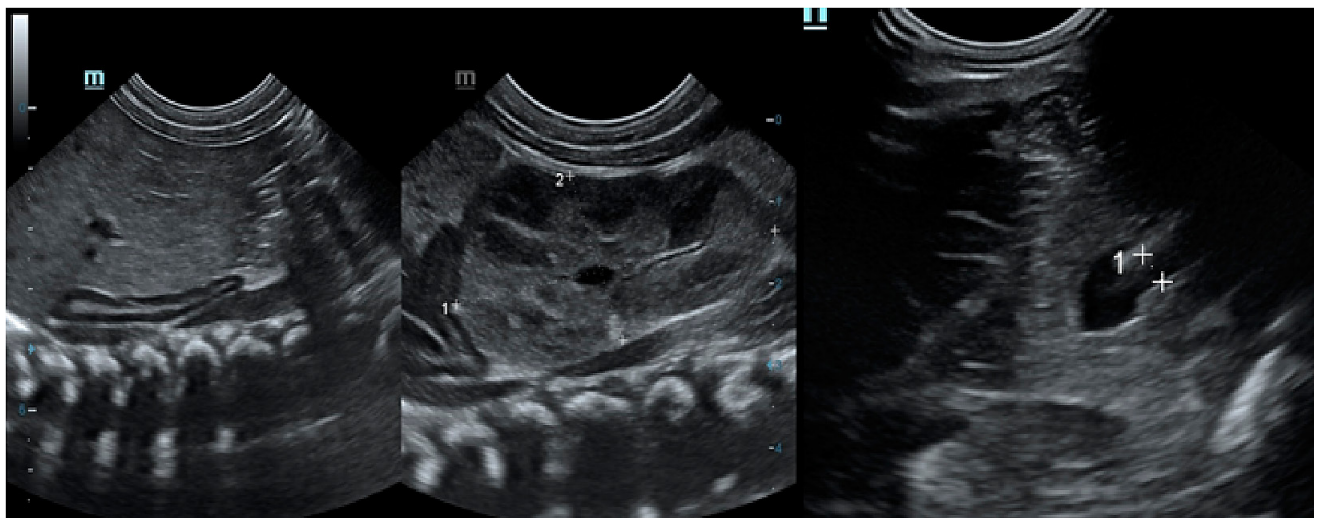


Figure 4. Case 3 (a, b), unilateral renal agenesis; (b) vermis hypoplasia

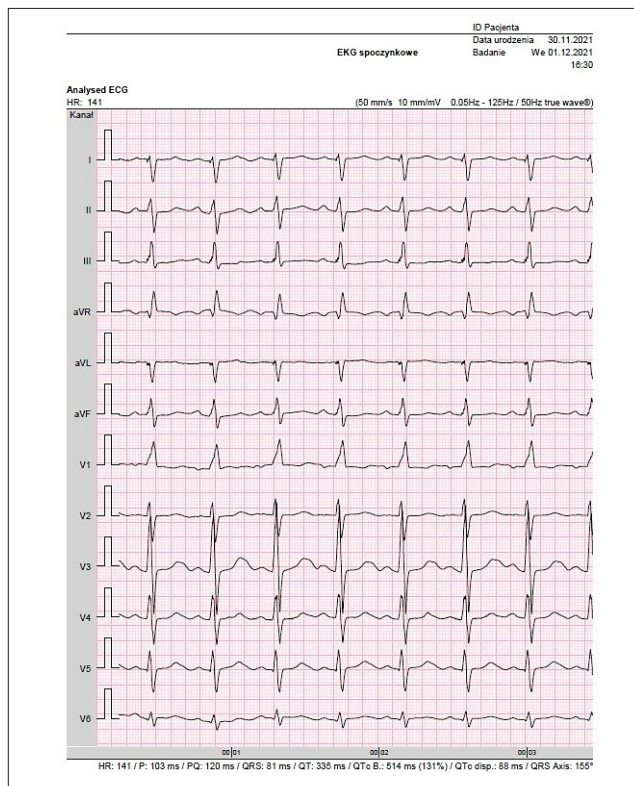


Figure 5. Case 4. ECG on first day of life with prolonged QTc due to hypocalcaemia

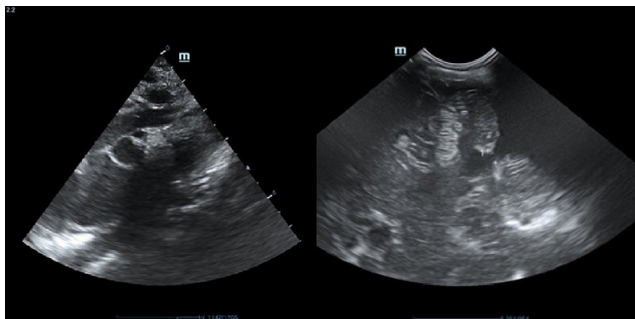


Figure 6. Case 4(a) interrupted aortic arch; (b) vermiform hypoplasia

In the period of three years, four children with confirmed 22q11.2 deletion were born at our Department, including two siblings. What is interesting is that the mothering Case 1 found out about her disorder only after she gave birth to the first child, when she was diagnosed for 22q11.2 deletion. The parents' examinations showed that the microdeletion in their daughter was inherited from the mother. In the course of her second pregnancy, when the mother was expecting a son, she did not want to undergo invasive genetic examinations. After the birth, both children demonstrated disorders in respiratory system adaptation. In the girl, the breathing disorders most probably resulted from pre-term birth, while the son was subject to an elective Cesarean section. Heart defects in the siblings should be classified as mild, and not significant in terms of haemodynamics. The heart defect in the girl (Case 1) involved the right aortic arch, with no impact on the neonatal and infancy periods. The boy was diagnosed with a heart defect at several levels, as it included both the anatomy of the aortic valve and muscular ventricular septal defect. The fact that the complexity of the boy's condition is greater than in the girl may be related both to the child's

gender, and the short time interval between pregnancies, which is an increasingly emphasized aspect.

As regards the siblings in question, the interval between pregnancies was six months. The International Prenatal Cardiology Collaboration group found a higher risk of recurrence of congenital heart disease (CHD) correlated with a shorter inter-pregnancy interval, with a median of 11 months compared to 24 months for the group of healthy foetals in subsequent pregnancy with CHD [5]. The siblings with diagnosed 22q11.2 deletion were subject to ultrasound examination which revealed thymus hypoplasia, while the ultrasound imaging of the brain and the abdominal cavity did not show any anatomic abnormalities. The monitored calcium levels were within the lower normal range, with no indication for supplementing this element. The children were initially bottle-fed, and then only breastfed, reaching normal weight-gain levels. Following the post-natal adaptation period, the suck-swallow-breathe synchrony was satisfactory in both children.

As regards the remaining two patients described in this paper, Cases 3 and 4, their cardiovascular defects were more severe than in the siblings, and more non-cardiac anomalies were also found. The patients were diagnosed with arterial cone defects, characteristic of 22q11.2 deletion. Congenital heart anomalies are present in approximately 75% of patients who had 22q11.2DS [6–8]. The most common were tetralogy of Fallot, ventricular septal defect with pulmonary atresia, persistent truncus arteriosus and interrupted aortic arch type B (Table 2). It is worth noting that the most common causes of death in 22q11.2DS were reported for cardiovascular patients with major congenital heart diseases who died at

Table 1. Baseline characteristics four described cases

	Case 1	Case 2	Case 3	Case 4
Gender	Girl	Boy	Girl	Boy
GA [weeks]	35	39	38	39
Birth weight [g]	2,180	3,200	3,180	3270
Apgar score	4-5-6-7	6-7-8-9	7-8-8-8	10-10-10-10
Respiratory insufficiency	Yes	No	no	no
Dysmorphism	yes	Yes	yes	yes
Single palmar creases	yes	No	no	no
Arythmia	no	no	no	no
QTc [ms]	410	480	No data	480-490
Heart anomaly	yes	yes	yes	yes
FO diameter[mm]	3	4	6	5
VSD	no	yes	yes	yes
Ao valve	tricuspid	bicuspid	Bicuspid TAC	Aortic valve stenosis
Aortic arch	RAA	normal	TAC type I	IAA type C
Thymus hypoplasia/aplasia	hypoplasia	hypoplasia	aplasia	aplasia
Hypocalcaemia	LLN	LLN	LLN	yes
Extracardiac anomalies	no	no	vermis hypoplasia Unilateral renal agenesis	Vermis hypoplasia polisplenia
Follow-up	normal	stable	death	survive

GA – gestational age; QTc – QT corrected for heart rate; FO – foramen ovale diameter; VSD – ventricular septal defect; RRA – right aortic arch; TAC – truncus arteriosus communis; IAA – interruption of aortic arch; LLN – lower limit of normal.

a significantly younger median age [9–10]. In the presented cases, the neonate with common truncus arteriosus died at the age of two months (Case 3). The cause of death was sudden infant death syndrome (SIDS). The patient was not subject to pathomorphological assessment.

Infants with 22q11.2DS may present a broad spectrum of other associated congenital anomalies listed in Table 2 [11–13]. In addition to heart structure defects significant in haemodynamic terms, patients 3 and 4 also had severe non-cardiac defects affecting the brain and abdominal cavity organs. They were also diagnosed with thymus aplasia. Infants with 22q11.2 deletion syndrome require extended diagnosis toward immunodeficiencies. Main problems arise from thymic aplasia or hypoplasia, followed by abnormal thymocyte numbers and function.

In clinical practice, it is recommended that newborn babies with thymic hypoplasia or aplasia are not given live vaccines in the initial days after their birth until immunology diagnostics have been completed [13]. The presented patients were vaccinated against hepatitis B, while tuberculosis vaccinations were rescheduled.

Hypoparathyroidism and subsequent hypocalcemia are present in 17%–60% of persons with 22q11.2DS and are typically most serious in the neonatal period. If untreated, low blood calcium levels can cause seizures in the neonatal period. Calcium homeostasis often normalizes with age, although the recurrence of hypocalcaemia in later childhood has been reported during illness [14–15]. None of the presented patients demonstrated any symptoms of seizures due to hypocalcaemia. Patient 4 had significantly low serum calcium level values and was given electrolytes intravenously, with good outcomes shown in check-up biochemical tests.

Neonates with 22q11.2DS are distinguished by their facial features. They have small, posteriorly-rotated ears, a small mouth, thin lips and wide-set eyes with hooded eyelids. Among other observed features are micrognathia, a deviated nose with a bulbous nasal tip and hypoplastic alae nasi. Facial dysmorphism becomes especially noticeable when there are abnormalities in the structure of the palate, such as a cleft palate or cleft and lip/palate. Due to the presence of these defects, newborns experience problems with sucking, swallowing and breathing. Defects of the central nervous system (meningeal hernia, abnormalities of the cerebral vessels, hydrocephalus) are occasionally described. Abnormalities in the structure and function of the genitourinary system, such as renal hypoplasia, cystic disease, hypospadias and cryptorchidism, are less common. Sometimes, gastrointestinal complications are observed, including oesophageal atresia, Hirschsprung disease, imperforate or ectopic anus, and intestinal malrotation [2].

Prenatal diagnosis should be considered in cases of high-risk pregnancy, especially when one of the parents is diagnosed with 22q11.2 deletion syndrome. If neither parent is genetically burdened, the risk of having another child with it is thought to be less than one in 100 (1%). If one parent has the condition, they have a one in two (50%) chance of passing it on to their child. Although deletions in 22q11 commonly have a maternal origin, maternal age does not act as an etiologic factor. Pregnancies which are characterized by an increased probability of having the chromosome 22q11.2 deletion syndrome are identified through genetic screening, for instance, through non-invasive prenatal testing (NIPT); however, the screening itself does not confirm the

Table 2. Clinical extracardiac finding of 22q11.2 deletion that may be evident prenatally and in the neonatal period

System affected	Examples
Palatal anomalies	Velopharyngeal incompetence (requires gastrointestinal tube feeding, posterior pharyngeal flap procedure) Submucosal cleft palate bifid uvula Cleft lip and palate
Genitourinary anomalies	Bilateral or unilateral renal agenesis Multicystic dysplastic kidneys Vesicoureteral reflux Inguinal hernia Hypospadias Cryptorchidism
Skeletal differences	Cervical spine anomalies Talipes Butterfly vertebrae Preaxial and postaxial polydactyly of the hands Postaxial polydactyly of the feet
Immunodeficiency-related	Thymic aplasia or hypoplasia T cell lymphopenia
Endocrinopathies	Neonatal hypocalcaemia due to hypoparathyroidism with neonatal seizures
Otolaryngologic anomalies	Laryngeal web/subglottic stenosis Trachea-oesophageal fistula Oesophageal atresia, tracheal atresia
Gastrointestinal problems	Feeding and swallowing difficulties Umbilical hernia Omphalocele Imperforate anus Intestinal malrotation or non-rotation Hirschsprung's disease Congenital diaphragmatic hernia (CDH)
Neurologic manifestations	Cavum septi pellucidi dilatation in ultrasonography Hypotonia Idiopathic seizures Microcephaly Polymicrogyria, heterotopias Chiari malformation Tethered cord Neural tube defects: myelomeningocele, anencephaly

Clinical findings in patients with 22q11.2DS based on a review of publications [2–3].

Table 3. Most commonly seen cardiovascular abnormalities associated with chromosome 22q11.2DS

Types of cardiovascular abnormalities	Examples of congenital heart defects
Conotruncal anomalies	Tetralogy of Fallot (ToF) Pulmonary atresia with or without ventricular septal defect (PA/VSD) Truncus arteriosus (TA)
Aortic arch anomalies	Interrupted aortic arch (especially type B) (IAA) Aortic arch double aortic arch or right aortic arch (RAA) Epiaortic vessel anomalies, including aberrant subclavian arteries (ASC) double aortic arch (DAA) vascular ring
Ventricular septal defects	Conoventricular septal defects (VSD) Muscular VSD

Cardiac anomalies in patients with 22q11.2DS based on a review of publications [2, 3, 8–11]

diagnosis. The signs that increase the probability that the infant has the condition include congenital heart defects, cleft palate, urinary track defects and other abnormalities shown on prenatal ultrasounds. Amniocentesis is usually carried out between the 15th and 20th weeks of pregnancy.

22q11.2 deletion syndrome is diagnosed based on cytogenetic testing. The method of fluorescence *in situ* hybridization (FISH) is used, using a probe that is a segment of DNA complementary to the deleted fragment. There is also an alternative method, the hr-CGH (high resolution comparative genome hybridization) test, which quantifies genetic material in specific sequences [2, 16].

CONCLUSIONS

Prenatal diagnostics of 22q11.2DS has numerous benefits for parents expecting children. The pregnancy period may prepare the family mentally and provide time for decisions related to pregnancy and the place where the baby is to be born. In such an event, it is recommended that the child delivery takes place in a tertiary referral level hospital with a neonatal intensive care unit. The coordinated care for a neonate with developmental disorders and a risk of immune system dysfunctions or hypocalcaemia, reduces the risk of morbidity and mortality.

Patients diagnosed in the neonatal period with 22q11.2 deletion syndrome may present symptoms ranging from mild to life-threatening conditions. The presented cases combined the features of dysmorphism, thymic hypoplasia and congenital heart defects of varying severity. In the neonatal period, the severity of the heart defect determines the survival rate in infancy. Children with 22q11.2 deletion syndrome will benefit from the care of a multidisciplinary medical team. After delivery, a cardiological consultation is necessary, as a newborn may require cardiac surgery. Electrocardiography may reveal significant disturbances in calcium metabolism that may prolong QTc. Ultrasonography is an effective screening method for the diagnosis of athymia or hypothyria, as a typical defect associated with 22q11.2 deletion syndrome.

It is worth emphasizing that 22q11.2DS has served as a model for explaining rare and common congenital anomalies and medical conditions, and may also become a platform for an improved understanding of these abnormalities, while at the same time creating opportunities for translational strategies throughout the lives of patients with 22q11.2DS, and individuals with the specified related features in the general population.

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