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CASES OF DIGEORGE SYNDROME

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ABSTRACT

DiGeorge syndrome is a primary immunodeficiency caused by the abnormal growth of the third and fourth pharyngeal pouches throughout prenatal development. It is typified by a triad: hypocalcemia due to hypoparathyroidism, some heart defects, and thymic hypoplasia or aplasia. This syndrome is associated with a microdeletion in the chromosomal region 22q11.2. DiGeorge syndrome together with other dysfunctions like velo-cardio-facial syndrome and Takao syndrome have overlapping traits. The symptoms are hidden under the name CATCH22. It describes signs like a cardiac defect, abnormal facies, thyme hypoplasia, cleft palate, hypocalcemia, and chromosome 22q11.2 deletions. Its incidence is estimated to be approximately 1:3000 live births. The disorder is inherited in an autosomal dominant pattern or arises from de novo mutation. 22q11.2 microdeletion is associated with an increased risk of developing mental diseases, including schizophrenia. In the general population, 1-2% of people suffer from schizophrenia. In DiGeorge syndrome this ratio is much higher, around 25-30%. Nowadays, the fluorescence in situ hybridization (FISH) is a gold standard method for the diagnosis of microdeletion syndrome. Currently, there is no effective therapy to prevent the development of the disease.
Keywords: DiGeorge syndrome, hypoparathyroidism, microdeletion, CATCH22, FISH.

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INTRODUCTION

The most frequent microdeletion syndrome in humans is DiGeorge syndrome. Theimproper migration and development of structures originating from the III and IV pharyngeal pouches (parathyroid glands and thymus) cause plenty of signs and symptoms.

Chromosome 22 is the second smallest chromosome in the human body and stores 1.6% of genetic material, but damage to it, is responsible for abnormalities in the development of many organs, including structures arising from the pharyngeal arches, heart and brain.

According to recent study, TBX1 is the major gene responsible for the phenotypic presentation of DiGeorge syndrome. Disturbance of its expression in the tissues of the pharyngeal arches and pharyngeal apparatus influence the onset of symptoms such as facial dysmorphism, palatal deformities, dental abnormalities, and eating and swallowing difficulties. It also controls the expression of a variety of growth factors. Characteristic features of DiGeorge syndrome were first described in 1828 but at that time no one knew that the collection of these descriptions formed a pattern. The syndrome was described by American physician Angelo DiGeorge in 1968. He described it as a triad of hypocalcemic tetany due to hypoparathyroidism, congenital heart disease and immunodeficiency. Nowadays, it is difficult to assess how many people are affected due to the wide range of symptoms – they can range from unnoticeable to severe.

EPIDEMIOLOGY OF DIGEORGE SYNDROME

The microdeletion of chromosome 22 occurs in 1 out of every 3000-6000 births. The disease affects men and women equally; regardless of ethnic background. Due to less common diagnostic methods in the past, the average age of diagnosis confirmation used to be around 4 years. Nowadays, modern genetic testing is available, which shortens the diagnostic time. Before 1990, many deletions were undetectable [1].

Early-onset DiGeorge syndrome is diagnosed before the age of ten. Late-onset disease refers to anomalies detected after the age of ten. The earlier the disease is diagnosed, the better the prognosis. Early detection of the mutation can help improve the quality of life. Many infants are born with severe heart defects, which, if left untreated, can result in infant mortality. Congenital heart defects are the most common serious developmental anomalies observed in cases of 22q11.2 deletion, occurring in approximately 75% of cases [2].

GENETIC ASPECTS OFT HE DISEASE

Several genes are responsible for the microdeletion syndrome, with the most important one being TBX1. This gene is closely associated with fetal development and is crucial in the formation of congenital defects. It can lead to congenital heart defects, hearing loss, facial deformities, and hypoparathyroidism. Symptoms vary depending on the location of the pathology. For example, dysfunction in exon 9C does not result in heart abnormalities [3]. The TBX1 gene provides the information necessary for the production of the T-box 1 protein, which is essential for the proper development of certain fetal parts. This gene is also responsible for the growth of bones, facial and neck muscles, and major arteries emerging from the heart [4]. The most common anatomical brain abnormalities associated with the absence of TBX1 include reduced brain and cerebellum volume, increased ventricular volume, altered brain gyrus morphology, and reduced gray and white matter in the parietal and temporal lobes [5].

Tab. 1

The table contains genes that are less closely associated with DiGeorge syndrome

Deleted gene	Hallmark
DGCR8	Liver haemorrhage, embryo death, cardiovascular abnormalities, cleft palate
CRKL	Reduction in T-lymphocytes production
CXCR4	Schizophrenia, autism spectrum disorders
PRODH	Schizophrenia and other psychiatric disorders
DGCR6	Schizophrenia and anxiety disorders

DIAGNOSTICS

Fluorescence in situ hybridization (FISH) is a cytogenesic technique based on fluorescently labeled DNA probes specific to a particular chromosomal region. The most commonly used probes are N25 and TUPLE1. This method is routinely used for detecting microdeletion and achieves up to 90% effectiveness [6].

Ultrasound examinations should be performed on every pregnant woman at least three times during a normal pregnancy. Ultrasound is effective in detecting cleft palate, which is characteristic of DiGeorge syndrome. Heart defects such as type B interrupted aortic arch, common arterial trunk, Tetralogy of Fallot, pulmonary valve atresia or stenosis, and ventricular septal defects are the most common prenatal indicators suggesting a chromosome 22 microdeletion [7].

CLINICAL PRESENTATION

HYPOCALCEMIA ASSOCIATED WITH HYPOPARATHYROIDISM

Hypoparathyroidism is caused by an embryological abnormality in the development of the pharyngeal pouches. Hypocalcemia affects nearly 60% of patients with DiGeorge syndrome. Significant hypocalcemia can lead to seizures, as well as respiratory issues such as bronchospasm and laryngospasm. Cardiological problems include bradyarrhythmia caused by QT interval prolongation and congestive heart failure due to impaired systolic function. Renal failure, including the development of chronic kidney disease and nephrolithiasis, are long-term consequences of hypoparathyroidism. Hypocalcemia also predisposes to an increased incidence of cataracts. Hypocalcemia can also be asymptomatic [8].

THYMIC DYSFUNCTION

IMMUNODEFICIENCY ASSOCIATED WITH PARTIAL DIGEORGE SYNDROME

Most individuals exhibit a partial form of immunodeficiency, leading to increased susceptibility to infections and sometimes immune disorders resulting in autoimmunity. In partial DiGeorge syndrome, the number of T lymphocytes ranges from nearly normal to almost completely deficient. Most individuals with the partial form of the disease do not experience opportunistic or life-threatening infections. Infections are typically sino-pulmonary in origin [9].

Tab. 2

Infections in Children over 9 years of age with 22q11.2 microdeletion. Source: PubMed, Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome)

Infection	Frequency (%)
Sinusitis	27
Otitis media	25
Bronchitis	7
Pneumonia	4

IMMUNODEFICIENCY ASSOCIATED WITH COMPLETE DIGEORGE SYNDROME

Complete DiGeorge syndrome is associated with athymia, which leads to a significant deficit of T lymphocytes. This type of syndrome affects only about 1-1,5% of the population with the chromosome 22 microdeletion. These patients experience severe combined immunodeficiency. According to one study, two-thirds of patients die within the first year of life due to infections [10].

CONGENITAL HEART DEFECTS

Tetralogy of Fallot is the most common congenital heart defect in DiGeorge syndrome. According to several researchers who studied pregnant women, Tetralogy of Fallot may account for up to 44.4% of all defects. Other defects include common arterial trunk, interrupted aortic arch, and ventricular septal defect.

FACIAL DEFORMITIES

Several dominant facial phenotypes are associated with the microdeletion syndrome. These features are difficult to identify in newborns but become noticeable in school-aged children. Ear anomalies are among the most recognizable features. Overfolding of the helix and protruding ears are common. The ears are usually small and low-set. A bulbous nasal tip with hypoplastic alae and a broad nasal bridge are also characteristic. The nose appears flattened. The lips are small and thin, micrognathia may be present. The eyes are small, slanted downward or upward, with drooping eyelids. Ocular hypertelorism is rarely observed [11].

PALATAL ABNORMALITIES AND FEEDING DISORDERS

Palatal defects are common in DiGeorge syndrome. According to one study, over 44% of patients with the chromosome 22 microdeletion syndrome have a cleft palate, with the majority of cases being submucosal cleft palate. About 80% of patients, in addition to cleft

palate, suffer from velopharyngeal insufficiency. During speech, the velopharyngeal valve does not close completely, leading to hypernasality and articulation problems. Nasopharyngeal reflux occurs in about 70% of patients due to velopharyngeal insufficiency. During swallowing, fluids regurgitate through the nose. Other gastrointestinal issues such as gastroesophageal reflux, esophageal motility disorders, and constipation may albo be present [12].

GROWTH HORMONE DEFICIENCY

T

he growth of children with DiGeorge syndrome should be monitored. Short stature is common among both children and adults with the microdeletion syndrome; however, growth hormone deficiency remains an important, treatable cause of this issue in this population. Growth hormone deficiency is most apparent during infancy and early childhood [13].

NEUROCOGNITIVE, BEHAVIORAL, PSYCHIATRIC DISORDERS AND LEARNING DIFFICULTIES

Children and adolescents with DiGeorge syndrome present a wide range of IQ levels. Typically, these patients demonstrate mild intellectual disability, while severe intellectual disability occurs in only about 1% of patients. Individuals with the microdeletion syndrome are significantly more prone to mental illnesses than the healthy population. The most common disorders are schizophrenia and schizoaffective disorder. In childhood, frequent diagnoses include attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders. Learning difficulties occur in almost all children. On the other hand, reading ability in most patients falls within the normal range [14].

TREATMENT

The treatment of hypocalcemia is determined based on whether it causes severe symptoms, such as seizures. If rapid correction of plasma calcium levels is necessary, an intravenous bolus of 10% calcium gluconate should be administered, followed by by an intravenous infusion over 24 hours. For a child who does not require urgent regulation of plasma calcium levels, oral calcium supplements should be given [15].

The use of vitamin D analogs, such as alfacalcidol or calcitriol, with calcium supplementation to prevent hypocalcemia by improving calcium absorption in the intestines is the standard treatment for hypoparathyroidism [15]. Oral magnesium supplementation is usually effective in treating hypomagnesemia. If hypomagnesemia symptoms are severe and oral supplementation is insufficient, intramuscular magnesium sulfate can be administered [15]. If a growth hormone deficiency is diagnosed, growth hormone therapy should be considered.

Palatoplasty is the first-line surgical method for treating velopharyngeal insufficiency in patients with submucosal cleft palate. This procedure is typically performed in children between 4 and 6 years old [16]. Patients with congenital athymia receive supportive care to reduce the risk of infections. A newborn should be placed in isolation with high-efficiency particulate air (HEPA) filters. All visitors must follow surgical hand-washing techniques and wear head coverings, masks, shoe covers, sterile gowns, and gloves to prevent the transmission of infectious diseases. Vaccination recommendations are based on the severity of the patient's immunodeficiency. Patients with partial DiGeorge syndrome may receive live vaccines. All live vaccines are contraindicated in patients with a complete T-cell deficiency [17].

Patients with DiGeorge syndrome have severe heart defects that require extensive surgical treatment. Surgery can be either palliative or corrective, and many patients may require reoperation. Patients are more prone to recurrent bacterial and viral infections and bronchomalacia. The chromosome 22 microdeletion can result in difficult intubation due to craniofacial anomalies [18]

CLINICAL CASES

CASE 1

A newborn boy presented with a flat nose with a broad base, bilaterally low-set ears, microstomia, right kidney agenesis, polydactyly, atrial and ventricular septal defects. He was admitted to the pediatric ward in the second week of life due to suspected DiGeorge syndrome. Calcitonin and PTH levels were significantly below normal. Chest X-ray revealed peribronchial inflammation, signs of pulmonary edema, suspected cardiomegaly, and hepatomegaly. The patient was given calcium gluconate and supplements: Vigantol and Vitacalcin. Serum calcium levels remained too low. After consulting an endocrinologist, the treatment was switched to alfacalcidol, which normalized calcium levels. Antibiotics (cefotaxime/gentamicin) were administered to treat the infection. Genetic testing using FISH confirmed a typical deletion on the long arm of chromosome 22. The surgeon recommended plastic surgery to remove the extra finger. No cellular immune deficiencies were observed in this patient, so vaccinations were not contraindicated during the first year of life. The child was regularly monitored and developed normally.

CASE 2

A 3-year-old boy, with no previous medical documentation, presented with his mother to the endocrinology clinic. The mother claimed that her son had been diagnosed with DiGeorge syndrome along with pulmonary valve atresia with a ventricular septal defect and collateral circulation. Chest deformity, significant microcephaly, hypotonia, and reduced subcutaneous fat were noted. Normal calcium ion levels were found. Serum IgA levels were below the normal range (<0.08g/l), indicating reduced immunity. PTH levels were normal. FISH diagnostics were performed to confirm the diagnosis. At the next visit, congenital hypoparathyroidism was also confirmed. The patient was given cardiotonics, calcium syrup, and Vigantol. During infections, antibiotics were administered orally.

CASE 3

A newborn was transported to the pediatric cardiology center immediately after birth due to a bluish-purple skin color, where pulmonary artery atresia was diagnosed. A catheterization procedure confirmed pulmonary valve atresia with a ventricular septal defect and multiple aortopulmonary collateral arteries

(MAPCAs). A stent was placed in one of the narrowed MAPCAs, but due to the number of narrowings and uncertain surgical outcomes, it was agreed with the parents that no further intervention would be performed. A 5-year-old boy was monitored by neurologists due to muscle atrophy and lack of proper development. Psychological assessment revealed intellectual disability, emotional instability, and delayed speech development. Scoliosis and short stature, inappropriate for the child's age, were also confirmed. During a consultation at age 15, the patient's height was 139.4 cm, and his weight was 45 kg; delayed puberty was noted. Growth hormone therapy was initiated. Hypopituitarism was also diagnosed. At age 18, the patient completed growth hormone therapy, reaching a height of 149.6 cm. Diagnostic testing for DiGeorge syndrome was performed, and the diagnosis was confirmed.

Tab. 3

Table of data regarding the growth of the observed patient.

Date of examination	Height (cm)
24.03.2015	124,5
20.08.2015	127,2
08.01.2016	127,6
10.10.2016	131
13.01.2017	133,6
16.10.2017	135,5
16.10.2018	139,4
08.09.2020	146,8
07.12.2020	147,1
06.12.2021	149,6

SUMMARY

DiGeorge syndrome is a genetic disorder associated with developmental and functional abnormalities in multiple organs, linked to a microdeletion on the long arm of chromosome 22. It is the most common chromosomal deletion in humans. The characteristic triad of chromosome 22 microdeletion includes hypocalcemia due to hypoparathyroidism, congenital heart defects, and thymic abnormalities. Additionally, there are many other health issues associated with this syndrome, such as palate anomalies, speech and feeding disorders, growth hormone deficiency, polydactyly, dental abnormalities, facial dysmorphia, as well as neurocognitive, behavioral, and psychiatric disorders.

It is important to remember that a visit to a genetic counseling clinic is necessary for the entire family to determine whether the mutation in the child occurred spontaneously or was inherited from one of the parents.

To detect the microdeletion, it is recommended to use a specialized diagnostic method. The most commonly used method is FISH (Fluorescence In Situ Hybridization), which can be performed during prenatal testing of the fetus.

Treatment requires consultation with multiple specialists and is complex. Some patients only require periodic check-ups, while others need multi-stage treatment that only partially improves their quality of life.

Based on the clinical cases included in this study, it is evident that there are significant differences among patients with DiGeorge syndrome. There is a wide spectrum of symptoms, but some occur more frequently. For example, congenital heart defects are present in 2 out of the 3 described patients. All patients exhibit at least one characteristic feature of the chromosome 22 microdeletion triad. In one patient, the main issue is immune deficiency, in another, hypocalcemia, and in the third, growth hormone deficiency. Based on this, it can be assumed that each case is unique and requires an individualized therapeutic approach.

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