DiGeorge Syndrome: Simultaneously Diagnosis of A Mother-Baby Pair With Great Clinical Variability

DiGeorge Sendromu: Büyük Klinik Değişkenlik Gösteren Bir Anne-Bebek Çiftinin Eşzamanlı Tanısı

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ABSTRACT

We report a female infant with complete DiGeorge syndrome who has craniofacial and skeletal abnormalities, feeding problems, cardiac defect, hypocalcemia induced seizure, thymic aplasia, and severe combined immune deficiency. Her mother also had a partial type of disease and was diagnosed at the same time with her baby. FISH analysis of both mother and the infant revealed a deletion in 22q11.2. This family's findings indicate that 22q11 deletion syndrome is a genetic condition with wide interfamilial and intrafamilial variability in clinical expression.

Keywords: Complete DiGeorge syndrome, clinical expression, severe combined immune deficiency, thymic aplasia

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ÖZET

Bu yazıda komplet DiGeorge sendromu tanısı almış, kraniyofasial ve iskelet anomalisi, beslenme problemleri, kalp defekti, hipokalsemik nöbeti, timik aplazi ve ağır kombine immune yetmezliği olan bir infantı sunmaktayız. Hastanın annesi ise parsiyel hastalıkla uyumlu bulgulara sahipti ve bebeği ile eş zamanlı olarak DiGeorge sendromu tanısı aldı. Anne ve bebekten çalışılan FISH analizinde 22q11.2 bölgesinde delesyon tespit edildi. Bu ailede anlatılan özellikler DiGeorge sendromunun aileler arasında ve aynı aile içinde dahi çok değişken klinik ekspresyon gösterebileceğini desteklemektedir.

Anahtar Sözcükler: Komplet DiGeorge sendromu, klinik ekspresyon, ağır kombine immune yetmezlik, timik aplazi

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INTRODUCTION

DiGeorge syndrome (DGS, 22.q11 deletion syndrome, 22q11DS, del22.q11) is caused by developmental defects in the third pharyngeal pouch and fourth pharyngeal arch and characterized by extremely variable clinical features including cardiac, thymus and craniofacial anomalies (1). Complete DiGeorge syndrome resembles a rare subtype of DiGeorge syndrome with thymic aplasia, profound T cell deficiency and poor prognosis without thymus or bone marrow transplantation (2). We present a case with complete DiGeorge syndrome whose mother also had the partial type of the disease and was diagnosed at the same time with her child at the age of 26. We want to highlight the huge variability in the clinical expression since subjects with full-blown clinical expression of the syndrome and mildly affected individuals can be found even in the same family and diagnosis of the disease can be delayed till adulthood. Given the fact, irrespective of the parental phenotype, both parents of patients should be tested for the disease to provide accurate genetic counseling to 22q11.2DS families.

CASE REPORT

A four-day-old, female infant born at 39 weeks gestational age was admitted to our neonatal intensive care unit for the complaint of poor feeding and weight loss. She was born as the first child of second-cousin consanguineous parents following an uncomplicated pregnancy. The birth occurred via C/S because of cephalopelvic disproportion. In detailed family history, the mother was 26 years old and had thrombocytopenia, hypothyroidism, and hypocalcemia for which she had used L-thyroxin and calcitriol but there was no diagnosed etiology for any of them. She also had a history of recurrent sinopulmonary infections and underwent surgery for the cleft palate correction that we finally learned after an insistent questioning for family history. Other remarkable clinical findings of the mother were a slightly long face, wide nasal bridge, bulbous nasal tip, and a hypernasal speech.

On physical examination, the patint was an asymmetric small-for-gestational-age (SGA) infant with a birth weight of 2660 g (3-10p) and head circumference of 34 cm (10-50p). She had dysmorphic features consisting of downslanting palpebral fissures, almond shape eyes, hooded eye lids, low-set antevert ears, left preauricular skin tag, tick and overfolded helices, bulbous nasal tip, micrognathia, camptodactyly of digits 2 through 5, long tapered fingers, ulnar deviation at both hands and the palate was intact (Figure1 and Figure2a-b). She had poor sucking reflex, mild truncal hypotonia and decreased spontaneous activities. She was below %15 percent of her birth weight, and there was also 1-2/6 systolic murmur best audible at the cardiac apex.

Figure 1. Left hand. Note camptodactyly and long tapered fingers.

Figure 2a. Facial appearance of the infant, frontal view.

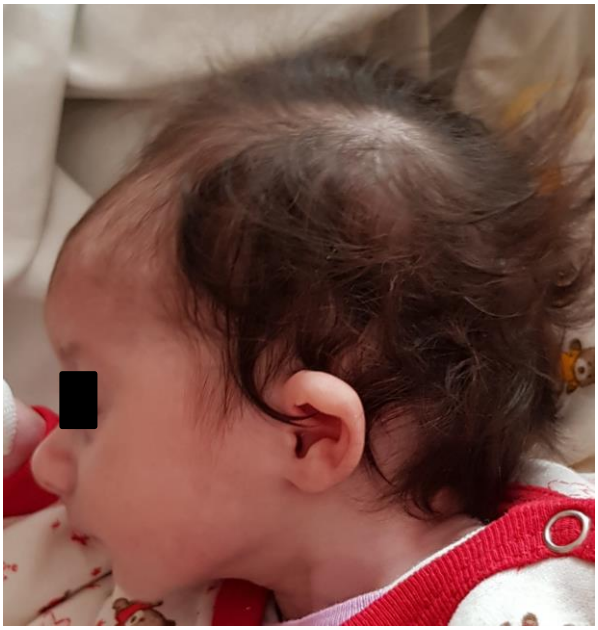

Figure 2b. Facial appearance of the infant, lateral view.

Her laboratory findings showed thrombocytopenia (86.000/mm³) and mildly elevated level of C-reactive protein (19 mg/dL) but blood cultures were negative. Other laboratory investigations such as capillary blood gas analysis, renal and hepatic function tests, blood glucose, and thyroid function test results were within normal ranges. TORCH screening test results were negative. Cranial and abdominal ultrasound scans were normal. Transthoracic echocardiography revealed one outlet ventricular septal defect (VSD) below the pulmonary valves and tree muscular VSDs in the apical part of the interventricular septum with dilated left ventricle. She was administered oral decongestive therapy with furosemide and captopril.

On the second day of admission, she manifested left-sided hemiclonic seizures lasted for approximately 15 seconds. Urgent laboratory investigation was conducted to assess biochemical abnormalities and neonatal infection.

She had hypocalcemia with a serum total calcium level of 5.6 mg/dl and ionized calcium level of 0.8 mEq/L and all other biochemical tests, cerebrospinal (CSF) fluid analysis, cranial imaging with ultrasound, magnetic resonance imaging (MRI) and diffusion MRI were normal. Seizure did not occur after serum calcium level was corrected with calcium replacement treatment and 400 IU/day vitamin D supplementation. No microorganism grew on CSF and blood cultures.

Under the light of suggestive signs and symptoms of cardiac abnormality, craniofacial abnormalities, skeletal abnormalities, and hypocalcemia, the diagnosis of DiGeorge syndrome was suspected. There was no thymic shade on chest radiograph and no thymic tissue was detected with mediastinum ultrasound which was consistent with thymic aplasia and also with complete DiGeorge syndrome. FISH analaysis with Vysis 32-190012 DiGeorge region N25 probe from mother and the infant revealed a deletion in 22q11.2. Serum parathyroid hormone concentration at the time of hypocalcemia was very low with the level of 9 pg/ml (normal range 15-65) as a result of parathyroid hypoplasia seen in the syndrome. Lymphocyte subset analysis revealed profound immunodeficiency with 2000 cell/mm^3 T cell count and undetectable CD3 + T cell (less than %0.1 percent of total T cells). Immunoglobulin A level was slightly low and other immunoglobulin levels were normal for age. Antimicrobial prophylaxis with trimethoprim-sulfamethoxazole and fluconazole got started. She was discharged after 30 days of hospitalization and referred to the immunology department of an outside tertiary institution for possible hematopoietic cell transplantation and long term follow-up. Her trombocyte count at discarge was normal.

DISCUSSION

DiGeorge syndrome is caused by developmental defects in the third pharyngeal pouch and fourth pharyngeal arch, and characterized by extremely variable clinical features, including cleft palate with feeding problems, cardiac, thymus, parathyroid, and craniofacial anomalies, cognitive and neuropsychological difficulties (1, 3-5). In the majority of cases (over 80%), it is caused by the microdeletion of 22q11.2. Recently, deletion of 10p13-14 and TBX1 mutation has been shown to be responsible for DiGeorge phenotype manifestations (6, 7). Embryopathy induced by retinoic acid and alcohol or maternal diabetes may also manifest in this phenotype (8). DGS, with an incidence at around 1:4000, is the most common type of contiguous gene syndrome in humans and is not a rare disease (9).

As seen in our patient, less than 1% of DGS patients present with complete athymia leading to a state of profound T-cell deficiency and this subtype is called complete DGS (cDGS). In typical forms of cDGS, T lymphocytes are absent or present in extremely low numbers (<50 CD3+ cells/mm3) and their function severely reduced with an absent or very low proliferative response to mitogens (10). Because of complete DGS resembles syndromic subtype of severe combined immunodeficiencies (SCID) and the degree of immunodeficiency does not correlate with other phenotypic features, immunologic status has to be assessed for every individual with a chromosome 22q11.2 deletion or with suggestive clinical features (11). These patients require allogeneic transplantation of the thymus tissue or hematopoietic stem cells to achieve immunological reconstitution otherwise the disease is always fatal within the first 2 years of life. As any SCID patient, they have to be isolated from other patients and receive antibiotic prophylaxis (2).

Because the heart, parathyroids, and thymus are involved, patients with this syndrome come to clinical attention with cardiac problems, hypocalcemic symtoms such as seizures and recurrent infections resulting from varying degrees of T cell dysfunction. Other findings to recognise the syndrome may include gastroesophageal reflux and feeding problems, speech delay, laryngomalacia, cleft lip and palate, absent kidney, facial abnormalities, limb abnormalities, conductive or sensorineural deafness, malformed ears (12).

Our patient had poor sucking and weight loss that made the family decide to admit our hospital. Among the very crowded physical and laboratory findings of her, the hypocalcemic seizure was the leading clue for us to achieve a correct diagnosis of DGS. More interestingly, the diagnosis was true for both the mother and the patient because after a great effort, we have finally succeeded to learn that the mother, who denied having any disease at the beginning, had a cleft palate correction surgery, recurrent sinopulmonary infection, hypocalcemia, thrombocytopenia and hypothyroidism.

Generally, 90% of DGS cases are caused by de novo or novel deletions by a random occurrence during fetal development. However, previous research has shown an autosomal dominant inheritance in 8 to 28% of cases. When one parent has DGS, the probability of their children having the syndrome is about 50% for each birth (13, 14). In the present case, the disease was inherited from the mother. Predicting the pattern of syndrome occurrence has vital importance to provide the family true genetic counseling and to estimate the risk of having an ill child for every pregnancy.

Hypocalcemia, due to absence or underdevelopment of parathyroid glands, was noted in 60% of subjects whom to have 22q11.2 deletions. It is considered one of the phenotypic characteristics of the DGS and most frequently manifests with seizures during the neonatal period as seen in our patient. Hypocalcemia may cause tremors, tetany, muscle cramps, stridor and arrhythmia (4, 15, 16). It can also occur during the late adolescent period or in the adult patients like the mother of present case. Hypocalcemia associated symptoms may be the only reason for a patient with 22q.11 deletion to seek medical care (17, 18).

Almost all subjects with DGS demonstrates facial anomalies with varying degrees of severity. Characteristic facial features include long face, malar flattening, hypertelorism, short palpebral fissures, a wide and prominent nasal root, a wide nasal bridge, a bulbous nasal tip, micrognathia, a small mouth, and small, low-set ears (19). The facial phenotype can easily be recognized as it was in our patient having down-slanting palpebral fissures, almond-shaped eyes, hooded lids, low-set antevert ears with tick, overfolded helices, bulbous nasal tip, and micrognathia. But in some patients, dysmorphic features may be subtle and may become more noticeable as the patient grow older (5). Our patient's mother had a slightly long face, wide nasal bridge, and bulbous nasal tip.

A variety of skeletal anomalies and deformations including scoliosis, vertebral malformations, limb anomalies, hypotonia, and ligamentous laxity have been detected in patients with deletion 22q.11 (20, 21). Our patient had upper limb abnormalities including camptodactyly and long tapered fingers. Camptodactilia seems to be a rare upper limb abnormality while most of the DGS patients having long tapered fingers as a characteristic diagnostic marker. Camptodactyly is seldom reported in patients with 22q11 deletion syndrome. Ming at al reported one patient with camptodactyly in a comprehensive review of skeletal anomalies in 108 patients with DGS (20). Oskarsdottir et al reported bilateral camptodactyly in 3 of 100 patients (22).

Aside from dysmorphic features, hypocalcemic seizure and immunodeficiency, one of the cardinal feature of our patient were multiple VSDs leading congestive heart failure. The prevalence of each congenital heart defects in DGS patients has already been reported in a review by Momma in 2010. In this report the most common diseases were conotruncal anomalies, including tetralogy of Fallot. VSD prevalence is reported at about %14, including every type. Multiple muscular VSDs were being the least common type in this review (23).

Considering 180 clinical signs and symptoms have been described to date, very high inter-individual variability and no correlation with the type of deletion and phenotype, diagnosis of 22q11DS could be missed in children, and the syndrome might be diagnosed during adulthood instead (22). Our patient and the mother excellently exemplify this as the baby is having almost all features of the syndrome, severe combined immunodeficiency and diagnosed at infancy while the mother has only mild dysmorphic features, recurrent sinopulmonary infections and some hematologic and metabolic abnormalities all of which remained undiagnosed till adulthood. Main presenting symptoms in adults can be developmental delays with psychiatric disorders, cardiac anomalies, hypoparathyroidism, autoimmune diseases, immune cytopenias, and hypothyroidism (16, 24). In 2014, Vogels et al reported a retrospective study performed on 65 individuals diagnosed with 22q11DS at adult age to identify adult patient groups in whom genetic testing is clinically warranted. The mean age at diagnosis in the total sample was 34 years (range 18–60). Presenting symptoms were familial occurrence, cardiac anomalies, psychiatric problems, intellectual disability, palatal abnormalities, and facial features respectively. Interestingly hypernasal speech with a history of feeding problems found to be the most commonly missed earlier symptoms of 22q11DS (25). The mother in the present case also had a hypernasal speech which could be due to both corrected cleft palate or mild nasopharyngeal hypotonia.

Thymus transplantation and hematopoietic cell transplantation are the two main choices for correcting underlying immunodeficiency in cDGS patients but patients with cDGA still present a therapeutic challenge since absence of T lymphocytes in these patients is the result of a lack of thymic environment.

Achieving long-term survival with hematopoietic cell transplantation has been published in studies. In 2010, Janda et al reported an overall survival rate of 41% with a median follow-up of 5.8 years for 17 patients transplanted with hematopoietic stem cell from 10 centers in Europe (26). Although it is not a worldwide available therapeutic option, thymus transplantation is now being the treatment of choice for cDGS patients, and it has shown to have very promising results. In a recent study reported by Davies et al in 2017, 12 patients with cDGS had thymus transplantation. Nine of the 12 patients were alive at a median follow-up time of 49 months. Clinical outcomes in survivors have generally been good and all had thymopoiesis (27). Because of thymus transplantation is not available in our county, our patient is referred to the immunology department of an outside tertiary institution for hematopoietic cell transplantation.

In conclusion, 22q11 deletion syndrome has a huge variability in the clinical expression since subjects with full-blown clinical expression of the syndrome and mildly affected individuals can be found even in the same family and diagnosis of the disease can be delayed till adulthood. Irrespective of the parental phenotype, both parents of patients should be tested for the disease to provide accurate genetic counseling to 22q11.2DS families. Assessing the immunological status of every individual with 22q11 deletion phenotype has vital importance since the underlying t cell deficiency can be fatal without thymus or hematopoietic stem cell transplantation in complete DiGeorge syndrome.

Conflict of interest

No conflict of interest was declared by the authors.

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