ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.044
Asthma Allergy Immunol 2023;21:59-63

CASE REPORT

Received: 07.06.2022 • Accepted: 19.09.2022
Online Published: 10.10.2022

# A Father and Son Diagnosed with DiGeorge Syndrome

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## ABSTRACT

DiGeorge Syndrome (DGS) is the most common of the microdeletion syndromes. Most deletions develop de-novo, while the rest are inherited in an autosomal dominant pattern. Although it is a common genetic disease, the diversity of clinical manifestations and the absence of typical clinical findings in a significant portion of the cases cause a delay in the diagnosis. In this case report, a father and son diagnosed with DGS are presented. The father's diagnosis of DGS was made after his child was diagnosed with the same disease. With these two cases, we aimed to emphasize the importance of careful evaluation of the parents of children diagnosed with DGS for the same disease.

**Keywords:** 22q11.2 microdeletion, Autosomal dominant, Cardiac anomalies, DiGeorge syndrome

## INTRODUCTION

DiGeorge Syndrome (DGS) is one of the most common genetic diseases characterized by developmental defects of the 3rd and 4th pharyngeal arches and neural crest cells. It usually occurs due to a deletion in the 22q11.2 region of the long arm of the 22$^{nd}$ chromosome (1). The prevalence of the syndrome is one in 4,000-6,000 live births. However, the clinical manifestations of DGS are very diverse and vary from patient to patient; therefore, the true incidence of the syndrome is not clearly known (1, 2). Most deletions (90-95%) develop spontaneously, while the rest are inherited in an autosomal dominant pattern (3).

Conotruncal heart defects, hypocalcemia, and thymus gland hypoplasia constitute the classic triad of the syndrome, while varying degrees of immunodeficiency, learning disabilities, endocrine disorders and characteristic facial appearance may also be present (4).

In this article, we present a father and son diagnosed with DGS, and aim to emphasize the importance of the careful evaluation of parents as well as children diagnosed with a genetic disease.

## CASE 1

A 4-month-old boy was diagnosed with pneumonia and treated at the hospital that he had previously presented at for cough and fever. However, he was referred to our institution for further evaluation upon achieving no adequate clinical improvement despite treatment.

He was born 2,565 grams at 37 weeks of gestation. His parents were nonconsanguineous and he had four healthy siblings. On physical examination, his body weight was 6 kg (10 percentiles), the height was 60 cm (3 percentiles), and head circumference was 41.5 cm (25 percentiles). Dysmorphic facial features including curved auricles, epicanthal fold, almond-shaped eye, and bulbous nasal tip were noticed (Figure 1). A systolic murmur was detected on the aortic focus. The remaining findings in the physical examination were unremarkable.

Laboratory investigation showed normal Hb (11.5 g/dL, normal: 9.5-14.1), low total lymphocyte count (2,400/mm$^3$, normal: 4,000-13,500/mm$^3$), normal neutrophil count (2,800/mm$^3$, normal: 1,500-8,500/mm$^3$). Serum IgG level was low (243 mg/dL, normal:

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280-666 mg/dl) while IgA (21 mg/dL, normal: 5-39 mg/dL) and IgM levels (20 mg/dL, normal: 19-94 mg/dL) were normal. Peripheral blood lymphocyte subsets revealed low CD3+CD16-56- T cells (50%, normal: 51-79%; absolute number: 1,200/mm$^3$, normal: 2,400-8,100/mm$^3$), and low CD3+CD4+ T cells (14%, normal: 31-54%; absolute number: 336/mm$^3$, normal: 1,400-5,200/mm$^3$). CD3+CD8+ T cells, B cells, and NK cells were normal. Parathormone, thyroid function tests, and other biochemical parameters were within normal limits.

The transthoracic echocardiography (TTE) showed a secundum atrial septal defect (ASD). In the thymus ultrasonography, the thymus tissue was seen as hypoplastic with a size of 8x4 mm. Abdominal ultrasonography was normal. Fluorescence in situ hybridization (FISH) analysis revealed chromosome 22q11.2 deletion. The diagnosis was confirmed as DGS.

**CASE 2**

A 38-year-old father, whose son (Case 1) was diagnosed with the same disease in our clinic, was evaluated for DGS. He had no history of severe and/or frequent infections, any operation, or hospitalization. His examination detected curved auricles, almond-shaped eye, and bulbous nose tip (Figure 1). The patient's auricle, lips and fingertips were cyanotic, and clubbing was present in the fingers. There was a 4/6 systolic murmur over the left sternal edge. The remaining findings in the physical examination were unremarkable.

Laboratory investigation showed high Hb (19.3 g/dL, normal: 13.5-17.5), normal total lymphocyte count (2,580/mm$^3$, normal: 1,000-4,800/mm$^3$), and normal neutrophil count (6,260/mm$^3$, normal: 1,800-7,700/mm$^3$). Immunological evaluation revealed normal serum IgG (1,040 mg/dL, normal: 944-1,505 mg/dl), IgA (251 mg/dL, normal: 65-176 mg/dL), IgM (93.4 mg/dL, normal: 86-175 mg/dL), IgG subclasses, and isohemagglutinin titers. Peripheral blood lymphocyte subsets revealed normal CD3+CD16-56- T cells (56.7%, normal: 58-82%; absolute number: 1,463/mm$^3$, normal: 1,100-4,100/mm$^3$), CD19+ B cells (9.8%, normal: 10-30%; absolute number number: 254/mm$^3$, normal: 200-1,400/mm$^3$), and NK cells (12.2%, normal: 8-30%; absolute number: 317/mm$^3$, normal: 200-1,000/mm$^3$) counts and percentages. Tetralogy of Fallot (FT) was detected in TTE. Abdominal ultrasonography was normal. FISH analysis showed the chromosome 22q11.2 deletion. The diagnosis was confirmed as DGS. The patient was referred to another hospital for cardiac pathologies. It was learned that the adult case underwent surgical intervention for cardiac pathology, is currently in good general condition, and is under clinical follow-up.

**DISCUSSION**

DiGeorge Syndrome is caused by a deletion in chromosome 22. The clinical manifestations of the disease are multisystemic and include mild to moderate immunodeficiency and cardiac anomalies of varying severity. Dysmorphic facial appearance is one of the most important findings seen in most patients (5). Although most cases are sporadic, an AD inheritance pattern is seen in approximately 5-10% of patients (3). The family of a boy diagnosed with DGS in our clinic was also examined for this disease. Typical phenotypic findings and FT were detected in the father, who was also later diagnosed with DGS.

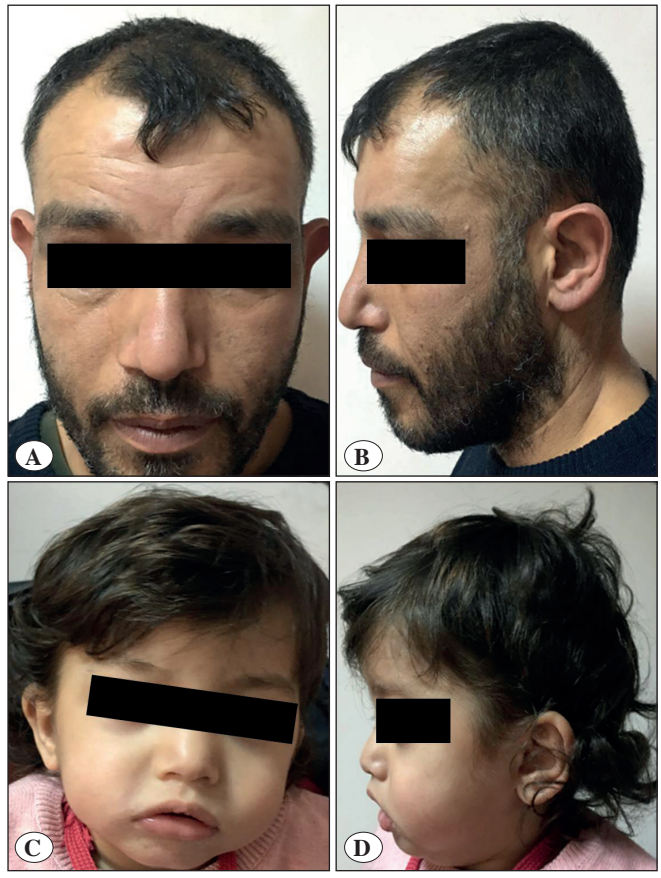


**Figure 1.** Father **(A,B)** and son **(C,D)** with typical facial appearance. **A)** Epicanthal fold and bulbous nasal tip, **B)** Round, low and curved auricles, **C)** Epicanthal fold and bulbous nasal tip, **D)** Round and curved auricles.

Many systems can be affected by DGS (Table I) (3). One of the most characteristic features of DGS is dysmorphic facial appearance, but these abnormalities are usually mild and therefore often overlooked (4). Typical facial findings are a long face, low ears, bulbous nose, almond-shaped eyes, hypertelorism, small mouth, and narrow palpebral fissures (5). Nasal anomalies are the most characteristic of all facial findings (6). In our cases, the son had a curved ear, epicanthal fold, and bulbous nose, while the father had curved ears, almond-shaped eyes, and a bulbous nasal tip.

**Table I. Clinical findings in patients with DiGeorge Syndrome**

| | |
|---|---|
| Cardiac anomalies | 49-83% |
| Tetralogy of Fallot | 17-22% |
| Interrupted aortic arch | 14-15% |
| Ventriculoseptal defect | 13-14% |
| Truncus arteriosus | 7-9% |
| Endocrine | 60% |
| Hypocalcemia | 50% |
| Growth hormone deficiency | 4% |
| Palatal anomalies | 69-100% |
| Velopharyngeal insufficiency | 27-92% |
| Cleft palate | 9-11% |
| Submucous cleft palate | 5-16% |
| Bifid uvula | 5% |
| Renal anomalies | 36-37% |
| Absent/dysplastic | 17% |
| Obstruction | 10% |
| Reflux | 4% |
| Ophthalmologic abnormalities | 7-70% |
| Posterior embryotoxon (anterior segment dysgenesis) | 69% |
| Tortuous retinal vessels | 58% |
| Skeletal abnormalities | 17-19% |
| Cervical spine anomalies | 40-50% |
| Vertebral anomalies | 19% |
| Lower extremity anomalies | 15% |
| Speech delay | 79-84% |
| Developmental delay in infancy | 75% |
| Developmental delay in childhood | 45% |
| Behavior/psychiatric problems | 9-50% |
| Attention deficit hyperactivity disorder | 25% |
| Schizophrenia | 6-30% |
| Neurologic | 8% |
| Cerebral atrophy | 1% |
| Cerebellar hypoplasia | 0.4% |
| Dental: Delayed eruption, enamel hypoplasia | 2.5% |

Endocrinological disorders, especially hypoparathyroidism, hypothyroidism, and growth hormone deficiency, are quite common in DGS cases. Choi et al. (7) have investigated 61 patients with DGS and found hypocalcemia in 20 (32.8%), hypoparathyroidism in eight (13.1%), and autoimmune thyroid disease in two (3.3%) patients. None of our patients presented here had any thyroid or parathyroid gland pathology.

In DGS, 75-80% of infants have a slight decrease in T-cell counts due to hypoplasia of the thymus, but T-cell counts in adults are usually normal. Naive and memory T cell deficiency in infancy and childhood also improve in adulthood with increasing age (6). T cell counts were low in our pediatric case, while normal in the adult case.

The humoral immune system is usually normal in DGS. IgA and IgM deficiency, mild hypogammaglobulinemia, and impaired antibody response to vaccines are the laboratory findings that can be encountered (6). While only hypogammaglobulinemia was detected in our pediatric case, serum Ig levels were normal in the adult case. During the follow-up of the pediatric case, the hypogammaglobulinemia persisted.

Approximately 75% of cases with DGS have conotruncal cardiac anomalies (8). Tobias et al. (9) examined the clinical features of 67 patients with DGS and found cardiac malformation in 51, including ventriculoseptal defect (VSD) in 26 patients, FT in 10 patients, ASD in 8 patients, and interrupted aortic arch in 7 patients. Some of the cardiac anomalies seen in DGS are lethal and result in intrauterine or early life mortality. Cases with cardiac anomalies such as VSD or FT may live to advanced ages. A DGS diagnosis can sometimes be made after FT is detected, especially in adult patients in whom the disease phenotype and clinical findings are not apparent (4). ASD was present in our pediatric case, and FT was found in our adult case.

Most of the patients diagnosed with DGS have de-novo mutation, and their parents are normal. Only 5-10% of patients have an AD inheritance. The risk of a parent with a deletion of having a diseased child is 50% for each pregnancy (3). Genetic counseling should be

given to diagnosed patients and their families (4). After the diagnosis, our adult case was informed, and genetic counseling was provided.

Learning difficulties and behavioral problems may sometimes be the only finding in patients with DGS. Behavioral problems and psychiatric disturbances may become more prominent with increasing age. Problems such as attention deficit and hyperactivity disorder, obsessive-compulsive disorder, depression, anxiety disorder, and poor social communication skills are frequently encountered in these patients. It should also be kept in mind that schizophrenia is 20-25 times more prevalent in these patients compared to the general population (10). It was learned that our patient could not complete his primary education and had an unsuccessful school history. Our preliminary evaluation of our patient did not reveal any findings suggestive of psychiatric disease. The patient was also referred to the psychiatry outpatient clinic for a more detailed clinical evaluation.

The most important factors affecting mortality in the patient group with DGS are conotruncal heart anomalies and severe immunodeficiency (6). Before the mid-1980s, the survival rate of patients with congenital heart anomalies used to be very low. Today, on the other hand, there is a large cohort of adults with these anomalies, and the majority of these patients are able to establish their own families (11). In the follow-up of patients, it is recommended to measure calcium levels once every 3-6 months during infancy and every 1-2 years thereafter. It is also recommended to examine the patients' thyroid functions and complete blood counts annually (12). Approaches such as prophylactic antibiotic therapy, intravenous immunoglobulin administration, and thymus transplantation have been suggested for immunocompromised patients (13).

Due to the diversity of clinical findings of DGS, patients who do not have classical findings may be overlooked. Especially adult cases need to be carefully examined for diagnosis. Some adult cases are diagnosed during the investigation of their children's disease (14). Our adult case was evaluated in the pediatric immunology clinic after his son was diagnosed with DGS, and then typical phenotypic features and a murmur on cardiac examination were detected, which aroused suspicion for the same syndrome. Our patient was diagnosed with DGS according to the FISH results.

In conclusion, although DGS is a common deletion syndrome, its diagnosis can often be missed. DGS should be considered in children with facial dysmorphism and developmental delay. The parents of children diagnosed with a genetic disease such as DGS should be carefully evaluated for the same condition.

**Disclosure of Interest**

The author declares that he has no competing interest.

**Funding Information**

No funding was received for this study.

**Acknowledgments**

We thank the parents of the patient for giving written consent for publication of this article.

**Authorship Contributions**

Concept: **Murat Özer, Caner Aytekin,** Design: **Murat Özer, Caner Aytekin,** Data collection or processing: **Murat Özer, Caner Aytekin,** Analysis or Interpretation: **Murat Özer, Caner Aytekin,** Literature search: **Murat Özer, Caner Aytekin,** Writing: **Murat Özer, Caner Aytekin,** Approval: **Murat Özer, Caner Aytekin.**

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