ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2023.2022-11-3

J Clin Res Pediatr Endocrinol 2023;15(3):285-292

# An Endocrinological Perspective on 22q11.2 Deletion Syndrome: A Single-center Experience

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### What is already known on this topic?

22q11.2 deletion syndrome is typically known for its triad of features, cardiac anomalies, immunodeficiency, and hypoparathyroidism. While it has been established that there is a typical facial appearance in this syndrome, many previously published articles and reviews have focused on philtrum and mouth anomalies.

### What this study adds?

Regarding typical facial features, drooping and/or swelling of the lateral eyelids (hooded eyelids), a long and prominent philtrum, and a thin upper lip are the reported findings that deserve special attention. There was no significant difference between permanent and transient hypoparathyroidism cases in terms of parathyroid hormone levels to predict permanent or temporary forms. Vitamin D deficiency is a risk factor for hypocalcemia and may be a cause of transient hypoparathyroidism in 22q11.2 deletion syndrome.

## Abstract

**Objective:** 22q11.2 deletion syndrome (22q11.2 DS) is the most common chromosomal microdeletion disorder. Associated problems in 22q11.2 DS may include cardiac abnormalities, immune dysfunction, facial dysmorphism, with endocrine, genitourinary and gastrointestinal problems, and developmental delay. The aim of this study was to evaluate and present all endocrinological findings of patients with 22q11.2 DS from a single center.

**Methods:** All participants had confirmed 22q11.2 DS by fluorescence in situ hybridization with hypoparathyroidism. Data were retrieved by retrospective review of patient records.

**Results:** A total of 17 patients were reviewed. On physical examination, all patients had similar dysmorphic features. The median age at diagnosis was 45 days (1 day-13 years). Most cases (64.7%, 11/17) were diagnosed with hypoparathyroidism incidentally after routine tests. At the time of diagnosis, mean calcium was 7.04 ± 0.80 mg/dL, phosphorus was 6.2 ± 1.1 mg/dL, and median parathyroid hormone (PTH) was 11.5 (3.7-47.6) ng/L. Transient hypoparathyroidism was detected in five cases (29.4%). There was no significant difference between patients with permanent or transient hypoparathyroidism regarding gender, age at diagnosis, calcium, phosphorus, and PTH levels. However, vitamin D levels were significantly lower in the transient group ($p = 0.036$). During follow-up, short stature, obesity, and type 2 diabetes mellitus were absent. Thyroid autoantibodies were detected in two patients with normal thyroid function tests. Despite there being no pathological short stature, final stature was shorter than the general population (mean height standard deviation score: -0.94 ± 0.83).

**Conclusion:** Hypocalcemia may be detected during acute illness in some cases where hypocalcemia appears at later ages. There was no significant difference between permanent and transient hypoparathyroidism cases in terms of PTH level. Recognition of the more specific facial findings is important to trigger investigation of genetic variants, additional anomalies, and for follow-up.

**Keywords:** 22q11.2 deletion syndrome, DiGeorge syndrome, hypoparathyroidism, hooded eyelids, immunodeficiency, Tetralogy of Fallot, vitamin D deficiency

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**Conflict of interest:** None declared
**Received:** 04.11.2022
**Accepted:** 01.04.2023

## Introduction

The 22q11.2 deletion syndrome (22q11.2 DS) is the most common chromosomal microdeletion disorder. This syndrome may involve cardiac abnormalities, immune dysfunction, facial dysmorphism, with endocrine, genitourinary and gastrointestinal problems, developmental delay, and neuropsychiatric disease. Chromosome 22q11.2 deletion may be diagnosed as DiGeorge syndrome, velo-cardio-facial syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, or Cayler cardio-facial syndrome, depending on the phenotype (1). Dysmorphic facial features are characteristic of 22q11.2 DS. Example of facial abnormalities include hooded eyelids, pseudoptosis of the upper eyelids, narrow palpebral fissures, telecanthus, hypertelorism, tubular nose, bulbous nasal tip, anteverted nostrils, low-set and posteriorly rotated ears, ear helix abnormalities, microtia, long/short philtrum, malar flattening, retrognathia, and chronic open mouth posture (2,3). Commonly associated endocrine disorders include hypocalcemia and hyperphosphatemia, due to parathyroid gland hypoplasia, growth retardation, obesity, skeletal anomalies, and thyroid dysfunction (4,5,6,7). It has been reported that short stature may occur due to cardiovascular abnormalities, recurrent infections due to immune deficiency, and nutritional problems might also become apparent (4). It is known that thyroid dysfunction may occur due to autoimmunity and thyroid hypoplasia (4). While certain features, such as immunodeficiency, cardiovascular anomalies, and hypoparathyroidism in the case of 22q11.2 DS have been commonly reported, few papers that present all the endocrinological abnormalities in 22q11.2 DS have been published (4,5,7,8,9).

The aim of this study was to retrospectively evaluate and present all endocrinological findings of patients with 22q11.2 DS from a single center.

## Methods

### Patients

All patients with 22q11.2 DS and endocrinological manifestations followed in Bursa Uludağ University Hospital, Clinic of Pediatric Endocrinology were included in the study. The study included only those patients with fluorescence in situ hybridization (FISH)-confirmed 22q11.2 DS who also had hypoparathyroidism. Patients without endocrinological findings (hypoparathyroidism, hypothyroidism, and/or short stature absent), genetically unconfirmed diagnosis and/or those over 18 years old were excluded. Age at diagnosis, clinical presentation, gender, and birth characteristics (week of gestation, birth height, birth weight) were retrospectively evaluated. Detailed laboratory analyses, including blood levels of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25 hydroxyvitamin D [25(OH)D], albumin, free T4 (fT4), free T3 (fT3), thyroid-stimulating hormone (TSH), thyroid autoantibodies [anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG) and TSH receptor antibody] were also evaluated. In addition, insulin-like growth factor-1 values were investigated in patients with height standard deviation (SD) score (SDS) $<-2$ during follow-up. Final height SDS in 5 patients and additional skeletal anomalies were evaluated. Cardiac malformation, immunodeficiency, and autoimmunity were also noted. Height and weight SDS values were calculated according to the reference values of Turkish children (10).

### Laboratory Analysis

TSH, fT4, fT3, and 25(OH)D values were analyzed with a Chemiluminescent Microparticle Immuno Assay method using the Abbott Architect Plus i2000 Immunoassay Analyzer device (Abbott, Abbott Park, Illinois, USA). Ca, P, PTH, and ALP values were measured by a spectrophotometric method using the Abbott Architect c-16000 Clinical Chemistry Analyzer (Abbott, Abbott Park, Illinois, USA).

### Genetic Analysis

Deletion of the chromosome 22q11.2 region was investigated using FISH, using Vysis DiGeorge Region LSI N25 Spectrum Orange/LSI ARSA Spectrum Green Probes (Abbott, Abbott Park, Illinois, U.S.A).

### Ethics

A consent form was filled out by all parents and participants. Written informed consent was obtained from the families of two patients who allowed the publication of clinical facial photographs. The study was approved by the Uludağ University Local Ethical Committee (approval number: 2021-19/22, date: 22.12.2021).

### Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 23.0 (IBM Inc., Armonk, NY, USA). To assess the significance of the differences between the groups, the normality of variables was tested with the Kolmogorov-Smirnov test. The Mann-Whitney U and chi-square tests were also used. Results were reported as median (interquartile range) or mean $\pm$ SD. A two-sided p value of $<0.05$ was considered statistically significant.

## Results

A total of 17 patients were included. The F/M (8/9) ratio was 0.88:1. The mean week of gestation was 38 weeks, birth weight was 3161±626 grams (0.22±1.15 SDS), and birth length was 48.5±3.7 cm (0.02±1.27 SDS). On physical examination, all cases had similar facial findings (Figure 1). The most striking facial findings of the patients were droopy and/or swollen lateral eyelid (hooded eyelids), telecanthus, bulbous nasal tip, anteverted nostrils, long and prominent philtrum, and thin upper lip.

All cases had hypocalcemia (n = 17), and the age at diagnosis was variable, ranging from 1 day to 13-years-old but with a median of 45 days. Eight cases were diagnosed in the neonatal period (8/17). Most cases (64.7%, 11/17) were incidentally diagnosed with hypoparathyroidism after routine tests. Hypocalcemia was diagnosed due to convulsions in two cases, tetany in two cases, and antenatal genetic diagnosis in two cases. The following serum levels were found at diagnosis: mean Ca 7.04 ± 0.80 mg/dL, P 6.2 ± 1.1 mg/dL, median PTH 11.5 (3.7-47.6) ng/L, ALP 158.5 (65-426) U/L and 25(OH)D 18.2 (5-36.1) µg/L. Ca treatment and calcitriol were started immediately after the diagnosis, and vitamin D supplementation was given to cases with vitamin D deficiency. Transient hypoparathyroidism was detected in five cases (29.4%) (Table 1). Three of these were diagnosed in the neonatal period during routine monitoring (Patients 1, 3, and 10) and all three had vitamin D deficiency. Maternal 25(OH)D level was only examined in the mother of patient 3, which was low (10.3 µg/L). Ca treatment was stopped on the 10$^{th}$, 35$^{th,}$ and 90$^{th}$ days. Hypocalcemia did not recur during follow-up. In the other cases (Patients 11 and 16) diagnosed at 14 months and 3.5 years, hypocalcemia was detected during major cardiac surgery. Ca treatment was discontinued at the 4$^{th}$ month and on the 20$^{th}$ day of treatment, respectively. No hypocalcemia was observed during follow-up.

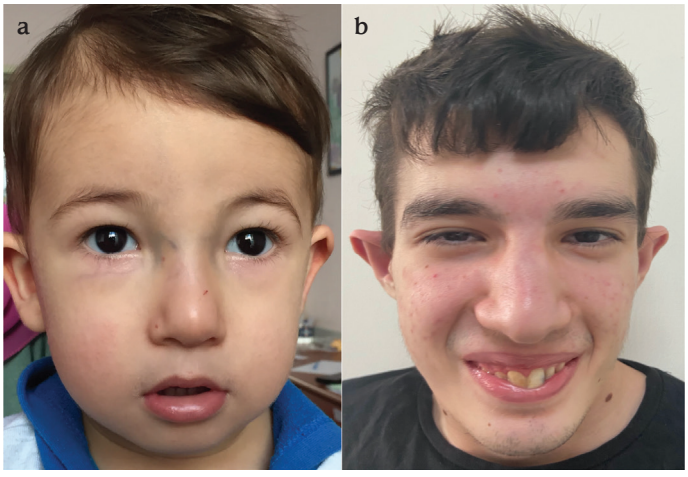


**Figure 1.** Typical facial appearance for 22q11.2 DS in different age groups a: Childhood (patient number: 15), b: Adulthood (patient number: 9)

*22q11.2 DS: 22q11.2 deletion syndrome*

The median age at diagnosis in the 12 patients with permanent hypoparathyroidism was 7.2 months (1 day to 13 years) (Table 2). In these patients mean Ca level was 7.1 ± 0.8 mg/dL, P 6.14 ± 0.98 mg/dL, median PTH 9.7 (3.7-47.6) ng/L, ALP 158.5 (87-426) U/L and mean 25(OH) D level were 19.9 ± 9.5 µg/L at diagnosis. All cases received calcitriol monotherapy, and no symptomatic hypocalcemia was detected during follow-up. No significant difference between permanent and transient hypoparathyroidism cases was found in terms of gender, age at diagnosis, Ca, P, or PTH (p = 0.523, p = 0.425, p = 0.689, p = 0.716 and p = 0.182, respectively). However, 25(OH)D levels were significantly lower in the transient hypoparathyroidism group, although this was only measured in 3/5 patients (p = 0.036).

Other endocrinological findings were evaluated. Short stature (mean height SDS: -0.94 ± 0.83), obesity, and type 2 diabetes mellitus were not found during follow-up, and the mean height SDS of the five patients who had reached their final height was -0.94 ± 0.94. Thyroid autoantibodies (anti-TPO and/or anti-TG) were detected in two cases with normal thyroid function tests. Two cases were diagnosed with primary hypothyroidism in the neonatal period, one by neonatal screening, the other in the intensive care unit.

While scoliosis was detected in three of the cases, no other skeletal anomaly was found. A Brown tumor was detected in the left parietal bone of the calvarium in a patient with scoliosis.

Some cardiac defect was observed in 13 (76%) cases (Tables 1 and 2). No significant difference was detected in height SDS between patients with and without cardiac anomaly (p = 0.400). While severe combined immunodeficiency was detected in one patient, B cell and/or T cell immunodeficiencies were reported in ten cases (58.8%). There was no significant difference in height SDS between patients with and without these immunodeficiencies (p = 0.983). Other rare additional findings are shown in Tables 1 and 2.

## Discussion

22q11.2 DS is the most common microdeletion disease with conotruncal anomalies. Cardinal findings are cardiac defect,

**Table 1. Diagnostic features of transient hypoparathyroidism cases**

| Patient number | Gender | Age at diagnosis with hypoparathyroidism (age) | Gestational age (week) | Birth weight SDS | Birth height SDS | Diagnosis | Calcium at diagnosis (mg/dL) | Phosphorus at diagnosis (mg/dL) | ALP at diagnosis (U/L) | PTH at diagnosis (ng/L) | 25(OH) D at diagnosis (µg/L) | Cardiac anomaly | Rare additional findings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 2 days | 39 | 1.98 | -1.1 | Incidentally | 7.5 | 4.6 | 169 | 19.5 | 6 | Terralogy of Fallot, ASD, right-sided aortic arch | No |
| 3 | F | 2 days | 38 | 0.37 | -0.55 | Incidentally | 6.5 | 7.4 | 202 | 12.4 | 8 | Truncus arteriosus, VSD, ASD | No |
| 10 | F | 1 day | $36^{+4}$ | 1.95 | 0.33 | Incidentally | 5.9 | 7.6 | 150 | 20.3 | 5 | VSD, Aortic coarctation, interrupted aortic arch, ASD | No |
| 11 | M | 14 months | 38 | N/A | N/A | During cardiac surgery | 7 | 5.9 | 65 | 38.8 | N/A | Terralogy of Fallot | Unilateral ureteropelvic stenosis, bifid uvula |
| 16 | M | 3.5 years | N/A | N/A | N/A | During cardiac surgery | 7.7 | N/A | N/A | N/A | N/A | Terralogy of Fallot, ASD | Strabismus and unilateral undescending testes |

M: male, F: female, N/A: not applicable/available, PTH: parathyroid hormone, ALP: alkaline phosphatase, SDS: standard deviation score, ASD: atrial septal defect, VSD: ventricular septal defect, 25(OH)D: 25 hydroxyvitamin D

immunodeficiency, and hypoparathyroidism (1,11). The physical examination findings of the cases are also important in the diagnosis, and typical facial findings have been highlighted (2,3). In the present study, droopy and/or swollen lateral eyelid (hooded eyelids), long and prominent philtrum, and thin upper lip were the most striking and helpful signs for rapid diagnosis.

Due to the abnormal parathyroid function, hypocalcemia has been reported to be the most common endocrine abnormality in 22q11.2 DS (12). Therefore, only cases with hypoparathyroidism were included in this study. In many studies, it has been reported that hypoparathyroidism is most common in the neonatal period (90-99%) and may be temporary due to the recovery of parathyroid function over time (5,7). In the present study, transient hypoparathyroidism was found in 29.4% of cases, 60% of which were diagnosed in the neonatal period. The lower incidence of neonatal transient hypoparathyroidism in this population may be due to not all facial findings being fully recognized, that there were no cardiac defects in some of the cases, and that there was no follow-up after the newborn period when the infant became normocalcemic. The detection of hypocalcemia after cardiac surgery in two of the patients, at 14 months and 3.5 years of age, with no previous symptoms shows that hypocalcemia may be evident during hypermetabolic states (7). It should be kept in mind that hypocalcemia may develop during acute illness in cases where hypocalcemia is not detected until older. In addition, cases with transient hypocalcemia should be carefully monitored for hypocalcemia in similar situations. A significant difference was found between the transient and permanent groups in 25(OH)D levels. Therefore, vitamin D deficiency was found to be a risk factor for hypocalcemia in 22q11.2 DS, especially the transient group. It seems reasonable that transient hypoparathyroidism would result from vitamin D deficiency in 22q11.2 DS, most probably due to the limited secretion capacity of the parathyroid gland. Therefore, it is important to avoid vitamin D deficiency in patients with 22q11.2 DS. It was noted that transient hypoparathyroidism due to vitamin D deficiency in 22q11.2 DS was previously reported in only one case in the neonatal period, secondary to maternal hypovitaminosis D

Table 2. Diagnostic features of persistent hypoparathyroidism cases

| Patient number | Gender | Age at diagnosis with hypoparathyroidism (age) | Gestational age (week) | Birth weight SDS | Birth height SDS | Diagnosis | Calcium at diagnosis (mg/dL) | Phosphorus at diagnosis (mg/dL) | Magnesium at diagnosis (mg/dL) | ALP at diagnosis (U/L) | PTH at diagnosis (ng/L) | 25(OH) D at diagnosis (µg/L) | Cardiac anomaly | Rare additional findings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | M | 45 days | 38 | -1.5 | -0.8 | Seizure | 6 | 4.9 | 1.8 | 181 | 6.5 | N/A | Tetralogy of Fallot, pulmonary artery hypoplasia | Unilateral renal agenesis and inguinal hernia |
| 4 | F | 10.5 years | 38 | -0.86 | N/A | Incidentally | 6.9 | 5.2 | N/A | 158 | 31 | N/A | Truncus arteriosus, VSD | No |
| 5 | M | 8 years | 39 | -0.11 | N/A | Incidentally | 8.9 | 5.6 | N/A | 157 | 9.1 | 18.27 | No | No |
| 6 | M | 12.5 years | 39 | N/A | N/A | Incidentally | 7 | 5.9 | N/A | 229 | 36.4 | 26.4 | No | Inguinal hernia |
| 7 | M | 13 months | $38^{+5}$ | -0.43 | N/A | Tingling in hands | 7.8 | 7.6 | 2 | 140 | 7.4 | 22.2 | No | No |
| 8 | F | 30 days | N/A | N/A | N/A | Seizure | 6.7 | 7.8 | N/A | 134 | 6.8 | 21.1 | Tetralogy of Fallot, ASD | No |
| 9 | M | 13.5 years | N/A | N/A | N/A | Incidentally | 5.8 | 6.4 | N/A | 128 | 10.6 | 24.7 | Dilatation of aortic root | Unilateral vanishing testes |
| 12 | F | 1 day | $34^{+1}$ | -1.02 | -1.38 | Incidentally | 6.6 | 7.3 | 3.1 | 426 | 4.1 | 8.9 | Truncus arteriosus | No |
| 13 | F | 11.5 years | N/A | N/A | N/A | Tingling in hands | 7.1 | 6.2 | N/A | 159 | 23.8 | 26.8 | No | No |
| 14 | F | 1 day | $39^{+1}$ | 0.77 | 2.51 | Incidentally | 6.8 | 5.3 | 1.9 | 195 | 47.6 | 7.9 | Pulmonary stenosis, VSD, ASD | No |
| 15 | M | 2 days | 40 | 0.24 | 0.28 | Antenatal | 7.8 | 6.3 | 2.6 | 177 | 3.7 | 7 | Truncus arteriosus, VSD, right-sided aortic arch | No |
| 17 | F | 1 day | $36^{+6}$ | 1.09 | 0.87 | Antenatal | 7.8 | 5.2 | 3.8 | 87 | 10.3 | 36.1 | Truncus arteriosus, VSD, pulmonary atresia | Cleft palate |

M: male, F: female, N/A, not applicable/available, PTH: parathyroid hormone, ALP: alkaline phosphatase, SDS: standard deviation score, ASD: atrial septal defect, VSD: ventricular septal defect, 25(OH)D: 25 hydroxyvitamin D

(13). Although it has been reported in a few studies that PTH levels may be undetectable in patients with permanent hypoparathyroidism (5), no significant difference was found in PTH levels between permanent and transient hypoparathyroidism cases in this study. PTH levels did not help predict transient or permanent hypoparathyroidism.

Growth retardation, thyroid dysfunction, and obesity are endocrinological problems seen frequently in 22q11.2 DS (4,5,7,8,9). Choi et al. (5) reported intrauterine growth retardation in 26.2% of their cases. In the present study, both birth weight and height were found to be in the normal reference range. It has been reported that the cause of growth retardation may be related to cardiac anomalies, recurrent infections, and nutritional problems, due to velopharyngeal anomalies (4,14). Levy-Shraga et al. (4) reported an association between heart defect and short stature, but not with recurrent infection and palatal defects. In the present study, no significant difference was detected in height SDS in patients with cardiac anomaly or T cell and/or B cell immunodeficiencies It is thought that this may be because cardiac surgery was quickly as early as possible, when necessary, in our cohort and there was no history of frequent infections in the cases with T cell and/or B cell immunodeficiencies. Goldberg et al. (14), suggested that short stature, seen in 30% of children, may be constitutional short stature since it is seen in only 10% of adults. These authors found no relationship between cardiac defect and short stature; growth hormone deficiency (GHD) was found in 4% of the cases. GHD was reported by Weinzimer et al. (11) in four cases, with growth hormone therapy improving the patient's final height. At the Children's Hospital of Philadelphia, short stature was reported in 10-40% of patients. GHD was found in some children below the 5th percentile for height (15). GHD was not detected in any patient in our cohort. This may be due to the larger number of patients in the earlier studies. Shprintzen et al. (16) described short stature in 39% of their patients. In another study, the height of patients who reached their final adult height was below -1 SDS (4). Habel et al. (17) and Tarquinio et al. (18) also reported that the cases were shorter than the general population. Similarly, in our study, the mean height was reported as -0.94 ± 0.83 SDS on follow-up, and the mean final height of five patients was -0.94 ± 0.94. Although no pathological short stature was seen in our cohort, the final stature of those reaching final height was indeed around -1 SD shorter than the general population.

Autoimmune (Graves and Hashimoto) and non-autoimmune (thyroid hypoplasia) thyroid diseases have been reported in 22q11.2 DS cases, affecting between 0.7-7% of patients (4,5,7,8,9). In the present study, thyroid autoantibodies were detected in two cases (11.7%) with normal thyroid function, and two cases (11.7%) were diagnosed with primary hypothyroidism in the neonatal period and started levothyroxine treatment. This rate is likely higher than the literature, which may suggests that thyroid diseases can be seen more frequently in 22q11.2 DS cases if hypoparathyroidism is present. But in our study, the number of the patient is very limited and there are many factors can affect thyroid metabolism. It has been reported that skeletal system anomalies, such as cervical spinal region anomalies, scoliosis, syndactyly, and patellar dysfunction are affect between 17-47% in 22q11.2 DS (19). In the present study, the rate of scoliosis was found to be similar to that in the literature. Previous reports have suggested that urogenital anomalies may affect approximately 30% of patients with 22q11.2 DS (20). There were four patients (23.5%) with urogenital anomalies in our study cohort. Thus, assessment of the skeletal system and investigation for urogenital anomalies should be performed in patients with 22q11.2 DS. Although the incidence of palate anomalies has been reported to be 69-100%, we found only two cases (11.8%) (19). Only patients with 22q11.2 DS and associated hypoparathyroidism were included in the present study, so the results may have been affected. Furthermore, given the low number of patients, our results may not accurately reflect the overall incidence of this anomaly.

### Study Limitations

It was not possible to access data for some cases due to technical issues. In addition, long-term follow-up of some cases was not performed in our hospital. Although studies into hypoparathyroidism were numerous, the frequency of other endocrine findings is not clear because of the paucity of data.

## Conclusion

This article describes various endocrine manifestations in patients with 22q11.2 DS. These findings suggest that careful endocrine evaluation is necessary for patients with this microdeletion syndrome, particularly those with hypoparathyroidism or thyroid dysfunction. It is known that many cases are diagnosed in the neonatal period, but some

may be missed due to transient hypocalcemia and loss of follow-up. These cases may present with hypocalcemia in acute hypermetabolic situations later in life. Therefore, patients with hypocalcemia in the neonatal period should be carefully monitored for 22q11.2 DS. Vitamin D deficiency was found to be a risk factor for hypocalcemia in 22q11.2 DS, especially in the transient group. It is important to carefully investigate cases presenting to pediatric endocrinology with hypoparathyroidism, especially in terms of cardiac and urogenital anomalies. Recognition of the more specific facial findings, particularly the hooded eyelids along with the better known dysmorphic features, may improve earlier diagnosis and trigger genetic diagnosis, screening for additional anomaly, and routine follow-up. The endocrinological findings and immunodeficiency types and prevalences in patients with 22q11.2 DS should be evaluated in larger series.

### Ethics

**Ethics Committee Approval:** The study was approved by the Uludağ University Local Ethical Committee (approval number: 2021-19/22, date: 22.12.2021).

**Informed Consent:** Written informed consent was obtained from the families of two patients who allowed the publication of clinical facial photographs.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Yasemin Denkboy Öngen, Erdal Eren, Concept: Yasemin Denkboy Öngen, Erdal Eren, Design: Yasemin Denkboy Öngen, Erdal Eren, Data Collection or Processing: Yasemin Denkboy Öngen, Erdal Eren, Analysis or Interpretation: Yasemin Denkboy Öngen, Şebnem Özemri Sağ, Şehime Gülsün Temel, Erdal Eren, Literature Search: Yasemin Denkboy Öngen, Erdal Eren, Writing: Yasemin Denkboy Öngen, Erdal Eren.

**Financial Disclosure:** The authors declared that this study received no financial support.

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