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

Denkboy Ongen Y et al. 22q11.2 Deletion Syndrome

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What is already known on this topic?
22q11.2 deletion syndrome is typically known for its triad of features, i.e., 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 does this study add?
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 PTH levels to predict permanent or temporary forms. Vitamin D deficiency is a risk factor for hypocalcemia and might be a cause of transient hypoparathyroidism in 22q11.2DS.

Abstract

Introduction: 22q11.2 deletion syndrome (22q11.2 DS) is the most common chromosomal microdeletion disorder. Associated problems with this syndrome may include cardiac abnormalities, immune dysfunction, facial dysmorphism, endocrine, genitourinary and gastrointestinal problems, and developmental delay. This study aims to evaluate and present all endocrinological findings of patients with 22q11.2 DS.

Materials and Methods: The seventeen participants in this study were all FISH confirmed 22q11.2 DS cases with hypoparathyroidism who had been followed in our Pediatric Endocrinology clinic.

Results: In the physical examination, it was observed that all patients had similar facial findings. The median age at diagnosis was 45 days (1 day-13 year). 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 PTH was 11.5 ng/L (3.7-47.6). Transient hypoparathyroidism was detected in five cases (29.4%). There was no significant difference between permanent and transient hypoparathyroidism cases regarding gender, age at diagnosis, calcium, phosphorus, and PTH. But vitamin D deficiency was noted in the transient cases. During follow-up short stature, obesity, and type 2 diabetes mellitus were not detected. Thyroid autoantibodies were detected in two patients with normal thyroid function tests. Pathological short stature was not seen in patients, but their final stature was shorter than the general population (mean height SDS: -0.94±0.83).

Conclusions: Hypocalcemia may detect during acute illness in some cases where hypocalcemia appears in advanced age. There was no significant difference between permanent and transient hypoparathyroidism cases in PTH levels. Recognition of the more specific facial findings mentioned in the study is important regarding genetic diagnosis, additional anomaly, and follow-up.

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

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Introduction

22q11.2 deletion syndrome (22q11.2 DS) is the most common chromosomal microdeletion disorder. This syndrome can involve cardiac abnormalities, immune dysfunction, facial dysmorphism, endocrine, genitourinary and gastrointestinal problems, developmental delay, and neuropsychiatric disease. Chromosome 22q11.2 deletion can 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 this are hooded eyelids, pseudoptosis of the upper eyelids, narrow palpebral fissures, telecanthus, hypertelorism, tubular nose, bulbous nasal tip, anteverted nostrils, low-set and posteriorly rotated ear, ear helix abnormalities, microtia, long/short philtrum, malar flattening, retrognathia, and chronic open mouth posture (2-3). Commonly associated endocrine disorders are hypocalcemia and hyperphosphatemia due to parathyroid gland hypoplasia, growth retardation, obesity, skeletal anomalies, and thyroid dysfunctions (4-7). 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 endocrinological abnormalities in such cases have been published (4,5,7,8,9).

This study aims to evaluate and present all endocrinological findings of patients with 22q11.2 DS.

Materials and Methods

Patients

Seventeen 22q11.2 DS cases followed in Bursa Uludağ University Hospital Pediatric Endocrinology clinic were included in the study. The study was based on those patients with fluorescence in situ hybridization (FISH) confirmed 22q11.2DS who had hypoparathyroidism. The patients with no endocrinological findings (hypoparathyroidism, hypothyroidism, short stature), genetically non-confirmed diagnosis and over 18 old age were excluded from the study. Age at diagnosis, clinical presentation, gender, and birth characteristics (week of gestation, birth height, birth weight) were evaluated. Detailed laboratory analyses such as calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), 25-OH vitamin 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 (IGF-1) values were studied in the cases with height standard deviation score (SDS) <-2 in the follow-up. Final height SDS and additional skeletal anomalies were evaluated. Cardiac malformation, immunodeficiency, and autoimmunity were also noted. Height and weight SDS values of the cases were determined according to the reference values of Turkish children (10).

Laboratory Analysis

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

Genetic analysis

Deletion of the chromosome 22q11.2 region was determined by FISH, using Vysis DiGeorge Region LSI N25 Spectrum Orange/LSI ARSA Spectrum Green Probes.

Ethics

A consent form was filled out by all parents and participants. Written informed consent was obtained from the families of 2 patients who accepted the use of their facial photographs. The study was approved by the local Ethical Committee (approval number: 2021-19/22).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences application for Windows, version 23.0 (IBM Co., 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±standard deviation. A two-sided p value of <0.05 was considered statistically significant.

Results

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). Regarding the 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 median age at diagnosis was 45 days (1 day-13-year-old). Eight cases were diagnosed in the neonatal period (8/17). Most cases (64.7%, 11/17) were incidentally diagnosed with hypoparathyroidism after the routine tests. Hypocalcemia was diagnosed with convulsion in 2 cases, tetany in 2
cases, and antenatal genetic diagnosis in 2 cases. The following levels were recorded at diagnosis: Mean calcium 7.04±0.80 mg/dl, phosphorus 6.2±1.1 mg/dl, median PTH 11.5 ng/L (3.7-47.6), ALP 158.5 U/L (65-426) and 25-OH vitamin D 18.2 μg/L (5-36.1). Calcium 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%, 5/17) (Table 1). Three of them were diagnosed at the neonatal period during routine monitoring (patient numbers: 1,3,10). In addition, vitamin D deficiency was noted in these 3 cases. Maternal 25-OH vitamin D level had been examined only patient’s mother, which was low (10.3 μg/L). Calcium treatment was stopped on the 10th, 35th and 90th days. Hypocalcemia did not recur in the follow-up. In other cases (patient numbers: 11 and 16) diagnosed at 14 months and 3.5 years, hypocalcemia was detected during major cardiac surgery. Calcium treatment was discontinued on the 4th month and 20th day of treatment, respectively. No hypocalcemia was observed in follow-up.

The median age at diagnosis in 12 patients with permanent hypoparathyroidism was 7.2 months (1 day-13-year-old) (Table 2). Mean calcium level 7.1±0.8 mg/dl, phosphorus 6.14±0.98 mg/dl; median PTH 9.7 ng/L (3.7-47.6), ALP 158.5 U/L (87-426) and 25-OH vitamin D level were 19.9±9.5 μg/L (5-36.1) at diagnosis. All cases received calcitriol monotherapy, and no symptomatic hypocalcemia was detected in the follow-up. No significant difference between permanent and transient hypoparathyroidism cases was found in gender, age at diagnosis, calcium, phosphorus, and PTH (p:0.523, 0.425, 0.689, 0.716 and 0.182). On the other hand, 25-OH vitamin D levels were significantly lower in the transient hypoparathyroidism group (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 detected in follow-up, and the mean height SDSs of the five patients who had reached their final height were -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.

While scoliosis was detected in 3 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. The cardiac defect was observed in 13 (76%) cases (Table 1 and 2). No significant difference was detected in height SDS between patients with and without cardiac anomaly (p:0.400). While total immunodeficiency was detected in one patient, partial immunodeficiency was shown in ten cases (58.8%). There was no significant difference in height SDS between patients with and without partial immunodeficiency (p:0.983). Other rare additional findings are shown in Table 1 and 2.

Discussion

22q11.2DS is the most common microdeletion disease with conotruncal anomalies. Cardinal findings have been reported as cardiac defect, immunodeficiency, and hypoparathyroidism (1, 14). The physical examination findings of the cases are essential in the diagnosis, and typical facial findings were highlighted (2-3). In our 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 22q11.2DS (11). 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 our study, transient hypoparathyroidism was found in 29.4% of cases, 60% of which were in the neonatal period. The lower incidence of neonatal transient hypoparathyroidism in this paper can be explained by the fact that not all facial findings were fully detected, there were no cardiac defects in some of the cases, and there was no follow-up after the newborn period due to the normocalcemic situation. The detection of hypocalcemia after cardiac surgery in two of the patients (14-month-old and 3.5-year-old) 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 an advanced age. 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 vitamin D levels. Therefore, vitamin D deficiency was found to be a risk factor for hypocalcemia in 22q11.2DS, especially the transient group. It can be predicted that transient hypoparathyroidism can be caused by vitamin D deficiency in 22q11.2DS, most probably due to the limited secretion capacity of the parathyroid gland. Therefore, it is important to avoid vitamin D deficiency in 22q11.2DS cases. It was noted that transient hypoparathyroidism due to vitamin D deficiency in 22q11.2DS was previously reported in only one case in the neonatal period secondary to maternal hypovitaminosis D (12). Although it has been reported in a few studies that parathormone levels may be undetectable in patients with permanent hypoparathyroidism (5), no significant difference was found between permanent and transient hypoparathyroidism cases in PTH levels in this study. PTH levels did not help predict transient and permanent hypoparathyroidism.

Growth retardation, thyroid dysfunction, and obesity are endocrinological problems seen frequently in 22q11.2DS (4,5,7,8,9). Choi et al. presented intrauterine growth retardation in 26.2% of their cases (5). In our
This article describes various endocrine manifestations in patients with 22q11.2DS. These findings suggest that thyroid diseases may be seen more frequently in 22q11.2DS cases if hypoparathyroidism is present. It has been reported that skeletal system anomalies such as cervical spinal region anomalies, scoliosis, syndactyly, and patellar dysfunction are seen at a rate of 17-47% in 22q11.2DS (19). In our study, the rate of scoliosis was found to be similar to that in the literature. It has been reported that urogenital anomalies are seen in approximately 30% of cases (20). Our study detected it in 4 cases (23.5%). The frequency of the skeletal system and urogenital anomalies showed that cases with 22q11.2DS should be screened closely. Although the incidence of palate anomalies has been reported in the literature as 69-100%, we found only 2 cases (11.8%) (19). The cases with hypoparathyroidism were included in the study, so the results may have been affected.

It is known that many cases are diagnosed in the neonatal period, but most of them can be missed due to transient hypocalcemia. 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 22q11.2DS. Vitamin D deficiency was found to be a risk factor for hypocalcemia in 22q11.2DS cases if hypoparathyroidism is present. It is important to carefully investigate those cases who applied to the endocrinology clinic with hypoparathyroidism, mainly in terms of cardiac and urogenital anomalies. Recognition of the more specific facial findings mentioned in the study is important regarding genetic diagnosis, additional anomaly, and follow-up. All endocrinological findings and immunodeficiency rates of 22q11.2DS cases need to be evaluated in a larger series.

**Conclusions**
This article describes various endocrine manifestations in patients with 22q11.2DS. These findings suggest that careful endocrine evaluations are 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 most of them can be missed due to transient hypocalcemia. 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 22q11.2DS. Vitamin D deficiency was found to be a risk factor for hypocalcemia in 22q11.2DS, especially the transient group.

**Strengths and limitations**
It was not possible to access data for some cases due to retrospective file scanning. In addition, long-term follow-up of some cases was not performed in our hospital. Although studies on hypoparathyroidism were numerous, the frequency of other endocrinological findings was not known precisely because of the lack of studies.
**Table 1: Diagnostic features of transient hypoparathyroidism cases**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Gender</th>
<th>Age at diagnosis with hypoparathyroidism (day)</th>
<th>Gestational age (week)</th>
<th>Birth weight SDS</th>
<th>Birth length SDS</th>
<th>Diagnosis</th>
<th>Calcium at diagnosis</th>
<th>Phosphorus at diagnosis</th>
<th>ALP at diagnosis</th>
<th>PTH at diagnosis</th>
<th>25-OH vitamin D at diagnosis</th>
<th>Cardiac anomaly</th>
<th>Rare additional findings</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>2</td>
<td>39</td>
<td>1.98</td>
<td>-1.1</td>
<td>Incidentally</td>
<td>7.5</td>
<td>4.6</td>
<td>169</td>
<td>19.5</td>
<td>6</td>
<td>T tetralogy of Fallot, ASD, right-sided aortic arch</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>2</td>
<td>38</td>
<td>0.37</td>
<td>-0.55</td>
<td>Incidentally</td>
<td>6.5</td>
<td>7.4</td>
<td>202</td>
<td>12.4</td>
<td>8</td>
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</tr>
<tr>
<td>10</td>
<td>F</td>
<td>1</td>
<td>36*4</td>
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<td>0.33</td>
<td>Incidentally</td>
<td>5.9</td>
<td>7.6</td>
<td>150</td>
<td>20.3</td>
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<td>n/a</td>
<td>During cardiac surgery</td>
<td>7</td>
<td>5.9</td>
<td>65</td>
<td>38.8</td>
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<td>Unilateral ureteropelvic stenosis, bifid uvula</td>
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<td>M</td>
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<td>n/a</td>
<td>During cardiac surgery</td>
<td>7.7</td>
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<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Tetralogy of Fallot, ASD</td>
<td>Strabismus and unilateral undescending testes</td>
</tr>
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</table>

*M: male, F: female, n/a: not applicable, PTH: parathormone, ALP: alkaline phosphatase, SDS: standard deviation score, ASD: atrial septal defect and VSD: ventricular septal defect
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Gender</th>
<th>Age at diagnosis with hypoparathyroidism (day)</th>
<th>Gestation age (week)</th>
<th>Birth weight SD S</th>
<th>Birth height SD S</th>
<th>Diagnosis of hypoparathyroidism</th>
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<th>Phosphorus at diagnosis</th>
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<td>2</td>
<td>M</td>
<td>45</td>
<td>38</td>
<td>-1,5</td>
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<td>Seizures</td>
<td>6</td>
<td>4,9</td>
<td>1,8</td>
<td>181</td>
<td>6,5</td>
<td>n/a</td>
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<td>Pulmonary artery hypoplasia</td>
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<tr>
<td>4</td>
<td>F</td>
<td>3832</td>
<td>38</td>
<td>-0,8</td>
<td>n/a</td>
<td>Incidentally</td>
<td>6,9</td>
<td>5,2</td>
<td>n/a</td>
<td>158</td>
<td>31</td>
<td>n/a</td>
<td>Truncus arteriosus, VSD</td>
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<tr>
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<td>M</td>
<td>2920</td>
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<td>5,6</td>
<td>n/a</td>
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<td>4562</td>
<td>39</td>
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<td>n/a</td>
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<tr>
<td>9</td>
<td>M</td>
<td>4745</td>
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<td>n/a</td>
<td>n/a</td>
<td>Incidentally</td>
<td>5,8</td>
<td>6,4</td>
<td>n/a</td>
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<td>12</td>
<td>F</td>
<td>1</td>
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<td>7,3</td>
<td>3,1</td>
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Table 2: Diagnostic features of persistent hypoparathyroidism cases
*M: male, F: female, n/a: not applicable, PTH: parathormone, ALP: alkaline phosphatase, SDS: standard deviation score, ASD: atrial septal defect and VSD: ventricular septal defect

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<th>Age</th>
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<th>1/O</th>
<th>0/8</th>
<th>7/8</th>
<th>5/2</th>
<th>3/8</th>
<th>87</th>
<th>10/3</th>
<th>36/1</th>
<th>Truncus arteriosus, VSD, pulmonary atresia</th>
<th>Cleft palate</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>F</td>
<td>1</td>
<td>36°6</td>
<td>1/09</td>
<td>0/87</td>
<td>7/8</td>
<td>5/2</td>
<td>3/8</td>
<td>87</td>
<td>10/3</td>
<td>36/1</td>
<td>Truncus arteriosus, VSD, pulmonary atresia</td>
<td>Cleft palate</td>
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</table>

Figure 1: Typical facial appearance for 22q11.2DS in different age groups a: Childhood, b: Adulthood