CASE

A 17-year-old female was referred to the endocrinology clinic after blood test results suggestive of hyperthyroidism. She had mild symptoms of thyrotoxicosis, including menstrual disturbance with intermittent palpitations and tremor. On examination, the patient was normotensive, tachycardic (100 beats/min), and of slim build with poor dentition. She had a small diffuse goiter without retrosternal extension or bruit. There was conjunctival injection but no evidence of lid lag or proptosis. Auscultation of the precordium revealed murmurs in systole and diastole consistent with mixed aortic valve disease.

The only child of healthy nonconsanguineous parents, the patient had previously been well. Her medical history included mild learning difficulties, a bicuspid aortic valve, recurrent urinary tract infections, and severe constipation as a child that required a colostomy, which was later reversed. Apart from an osmotic laxative, she received no other regular medication. A recent echocardiogram had demonstrated a bicuspid aortic valve with good flow and minor regurgitation.

Biochemically, the patient had an undetectable serum concentration of thyroid-stimulating hormone (TSH) \(<0.03\) mIU/L (reference interval, 0.3–5.6 mIU/L) and an increased concentration of free thyroid hormone (fT4) \(43\) pmol/L (3.3 ng/dL); reference interval, 7.5–21.1 pmol/L). Her baseline serum concentrations of total calcium \(2.27\) mmol/L (9.08 mg/dL) and phosphate \(1.26\) mmol/L (3.9 mg/dL) were both within their respective reference intervals (2.20–2.60 mmol/L and 0.75–1.36 mmol/L, respectively). The serum albumin concentration was \(41\) g/L (reference interval, 35–50 g/L), and the magnesium concentration was \(0.71\) mmol/L (reference interval, 0.74–1.00 mmol/L). The results of her other biochemical tests were unremarkable. An immunologic analysis demonstrated increased thyroid peroxidase antibodies (582 IU/L; reference interval, 0–60 IU/L) and increased TSH receptor antibodies (6.9 U/L; reference interval, 0–1.5 U/L), confirming Graves disease. Thyroid imaging revealed a diffusely enlarged thyroid gland, with no visible parathyroid tissue apparent on ultrasound and MRI evaluations.

After daily treatment with 30 mg carbimazole and 25 mg atenolol, the fT4 concentration in the patient decreased as expected (fT4, 19.2 pmol/L; TSH, 0.03 mIU/L). Concomitantly, the patient developed asymptomatic hypocalcemia (calcium, \(1.72\) mmol/L (6.88 mg/dL)). The total 25-hydroxyvitamin D concentration was 38 nmol/L (reference interval, 15–100 nmol/L), and her serum magnesium concentration was 0.87 mmol/L (reference interval, 0.74–1.00 mmol/L). Both were within their respective reference intervals. The serum phosphate concentration was 1.28 mmol/L (reference interval, 0.9–1.35 mmol/L), and the albumin concentration was 48 g/L (reference interval, 35–50 g/L). The parathyroid hormone (PTH) concentration was also within the reference interval \(4.8\) pmol/L (4.8 ng/L; reference interval, 1.6–9.3 pmol/L) and thus appropriately normal given the degree of hypocalcemia. A diagnosis of hypoparathyroidism was made, and the patient was treated with 0.5 \(\mu\)g alfacalcidol daily. The calcium concentration briefly normalized (Table 1).

After this improvement, the patient stopped complying with her carbimazole and alfacalcidol treatment regimen, and the results of thyroid function tests returned to near pretreatment concentrations (fT4, 58.4 pmol/L (4.5 ng/dL); TSH, <0.03 mIU/L; calcium, 2.34 mmol/L (9.36 ng/dL); Table 1). With improved patient compliance, the fT4 results improved, approaching euthyroidism. The patient eventually achieved a normocalcemic state (fT4, 13.5 pmol/L (1.0 ng/dL); calcium, 2.35 mmol/L (9.4 mg/dL)). More recently, compliance has been a concern with recurrent increased fT4 concentrations (Table 1).
The patient gave full written consent for the use of her clinical information and laboratory tests for the purposes of submission of a case report to the medical literature. She has very mild learning difficulties but was able to understand, process, and retain the information given.

**DISCUSSION**

The underlying cause of the hypoparathyroidism was elucidated after several further laboratory investigations were undertaken for the patient. A fluorescence in situ hybridization analysis revealed a deletion at 22q11 consistent with DiGeorge syndrome. An echocardiography examination revealed a bicuspid aortic valve, but no other cardiac abnormality. A lymphocyte analysis showed typical lymphocyte subsets.

This report illustrates that a dual pathology may obscure a diagnosis. In this case of previously undiagnosed DiGeorge syndrome, the hypercalcemic effect of uncontrolled thyrotoxicosis masked the underlying diagnosis of hypoparathyroidism. Treatment of the thyrotoxicosis allowed the underlying hypoparathyroidism to be identified and led to the investigation for DiGeorge syndrome. Biochemical testing was fundamental in elucidating the multiple diagnoses in this case.

Calcium metabolism is under strict homeostatic control through the coordinated actions of PTH and activated vitamin D. Hypoparathyroidism is an uncommon condition characterized by inadequate PTH secretion, which leads to hypocalcemia. The fact that patients may experience few symptoms even at remarkably low calcium concentrations can hinder diagnosis. In this case of the rare combination of hypoparathyroidism and thyrotoxicosis, hypocalcemia became evident only upon treatment of the thyrotoxicosis. Interestingly, this patient had had slightly low and low-normal calcium results in childhood. These findings had been attributed to her stoma and appeared to normalize after oral calcium administration.

Thyrotoxicosis has been known for many years to cause a syndrome of hypercalcemia (1). The mechanism for hypercalcemia in thyrotoxicosis has yet to be fully elucidated, but one possibility is that it may be due to increased bone resorption (2) causing calcium release into the circulation and increased urinary excretion of calcium, phosphate, and hydroxyproline. The association between long-standing thyrotoxicosis and osteoporosis adds weight to the likelihood of this potential mechanism. Another possibility is that thyrotoxicosis may have some direct or indirect effect on the parathyroid glands. Although there is evidence that the hypercalcemia of thyrotoxicosis occurs independently of the parathyroid axis (3), increased PTH concentrations that normalize with successful treatment have been described for patients with thyrotoxicosis (4).

The degree of hypercalcemia in thyrotoxicosis patients is extremely variable. A majority of patients have minor fluctuations in the calcium or phosphate concentration, but some patients have markedly symptomatic disease. Occasionally, the hypercalcemia can be a presenting feature of the disease. In a recent series, 2 patients were found to have hyperthyroidism after an investigation for hypercalcemia (5). The hypercalcemic effect of thyrotoxicosis in the present patient with hypoparathyroidism produced a serum calcium concentration within the reference interval.

**Table 1. Chronological changes in the serum concentrations of total calcium and fT4 as treatment progressed.**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference interval</th>
<th>Months after presentation</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>0.3–5.6</td>
<td>≤0.03</td>
</tr>
<tr>
<td>fT4, pmol/L</td>
<td>10–21</td>
<td>43.0</td>
</tr>
<tr>
<td>Total calcium, mmol/L (mg/dL)</td>
<td>2.2–2.6 (8.8–10.4)</td>
<td>2.27 (9.08)</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>0.9–1.35</td>
<td>1.26</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35–50</td>
<td>41</td>
</tr>
</tbody>
</table>

*At presentation of thyrotoxicosis, treatment with carbimazole caused fT4 to improve, with a significant reduction in calcium. Concomitant treatment with alfalcaldol caused calcium concentrations to normalize. Treatment noncompliance 12 months after presentation caused a thyrotoxicosis relapse, which was treated to achieve euthyroidism and normocalcemia. The most recent results demonstrate recurrent thyrotoxicosis, which may also be related to noncompliance. Values in boldface are outside the reference interval. NA, data not available.*
likely predated the thyrotoxicosis. None of these patients were tested for 22q11 deletions.

A more recent report described a case series of 4 children who presented early in life with speech disturbance, symptomatic hypoparathyroidism, thyrotoxicosis, and appreciable congenital heart disease due to underlying 22q11.2 deletion (9). A subsequent report described a patient with DiGeorge syndrome with 22q11 deletion (10) who presented at age 18 years with symptoms of hypocalcemia and thyrotoxicosis. The authors referred to this case as “partial” DiGeorge syndrome because the parathyroid and thymic abnormalities were not as severe as those documented in other cases.

The present case is the first description in the literature of a patient with 22q11 deletion who presented with concomitant symptomatic thyrotoxicosis and asymptomatic hypoparathyroidism and who had a serum calcium concentration that was paradoxically within the reference interval. Treatment of the thyrotoxicosis permitted the identification of the underlying hypoparathyroidism and prompted investigation for DiGeorge syndrome.

DiGeorge syndrome, which occurs at a frequency of about 1 in 4000 live births, is caused by a deletion on chromosome 22. The deletion is usually due to spontaneous mutation, but autosomal dominant inheritance patterns have also been described. The disease has a highly variable expression. DiGeorge syndrome and the related conditions velocardiofacial syndrome and conotruncal anomaly face syndrome are characterized by the “CATCH-22” features: cardiac defects, abnormal facies, thymic dysfunction, cleft palate, and hypocalcemia caused by a deletion on chromosome 22. Thymic dysfunction causes an abnormal maturation of T cells and an increased susceptibility to infection. Many affected children die in the perinatal period from congenital cardiac disease or severe infections, whereas other affected patients survive into adolescence with few symptoms. The current case is of a patient with an atypical presentation of features at the milder end of the DiGeorge spectrum. Diagnosis requires cytogenetic testing, which is prompted by the clinical features.

The mechanism for the development of thyrotoxicosis in DiGeorge syndrome is unclear, but several reports have demonstrated the presence of thyroid antibodies, findings that indicate a likely autoimmune etiology (9, 10). Paradoxically, these patients with a reduced immune function thus appear to develop likely autoimmune-mediated thyrotoxicosis. T-regulatory cell dysfunction due to a lack of thymus may lead to the production of autoimmune phenomena, with autoantibody production. The reason the thyroid is the usual target endocrine organ in this condition may be that the third and fourth pharyngeal pouches, which are the embryologic source of all of the thymus and the 4 para-thyroids, are also involved in part of thyroid organ development.

CONCLUSIONS

We describe the 10th case of DiGeorge (22q11 deletion) syndrome with hypoparathyroidism and thyrotoxicosis to be published. Unusually, in this case, the dual endocrine pathology presented with a calcium concentration that was paradoxically within the reference interval. Treatment of the thyrotoxicosis permitted identification of the underlying hypoparathyroidism and led to further investigation that confirmed DiGeorge syndrome. The dual pathology was demonstrated several times during periods of the patient’s noncompliance with treatment.
their analysis and interpretation of the fluorescence in situ hybridization results.

References


Commentary

Donald Zimmerman*

This case describes an important metabolic effect of increased thyroid hormone concentrations on calcium and bone as well as subtle T-cell defects known to occur in the setting of DiGeorge syndrome (also known as DiGeorge sequence). DiGeorge sequence is caused by chromosomal deletions at 22q11.2, which can be transmitted with an autosomal dominant pattern of inheritance; new mutations constitute 90% of cases. Calcium metabolism is regulated by parathyroid hormone and by vitamin D. Physiological concentrations of thyroid hormone do not direct calcium homeostasis, but high concentrations often produce important perturbations.

In 1891, von Recklinghausen described bone abnormalities in hyperthyroidism. In the 1920s, investigators at Massachusetts General Hospital observed increased calcium excretion in hyperthyroidism and that it occurred independently of parathyroid hormone.

Hypercalcemia was observed in thyrotoxic patients in the 1930s and 1940s. Twenty-seven percent of hyperthyroid patients have an increased total calcium concentration, and 47% have increased ionized calcium (1). Parathyroid hormone is suppressed in these patients.

We described a patient who had hypoparathyroidism, conotruncal cardiac abnormalities, and developmental delay suggestive of DiGeorge sequence and who became hypercalcemic with Graves disease (2). DiGeorge sequence includes congenital conotruncal cardiac defects, palate abnormalities, hypoplastic thymus, T-cell immune defects, hypoparathyroidism, and learning and psychiatric problems. Bicuspid aortic valve, which is described in the report of Meek et al., has been described in only a single patient with this condition.

T-cell deficiency is occasionally severe in DiGeorge sequence. Less severe immune defects are more common and include autoimmune diseases, which occur in 30% of patients (3). Autoimmune thyroid diseases occurring in DiGeorge sequence prominently include Graves disease.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References