Endocrine aspects of the 22q11.2 deletion syndrome

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Hormonal disorders are common in patients with a 22q11.2 deletion. While hypoparathyroidism was the first endocrine disturbance documented in the DiGeorge syndrome, growth hormone deficiency, hypothyroidism, and hyperthyroidism are now known to occur in patients with a 22q11.2 deletion. This review briefly summarizes our current understanding of the spectrum of endocrinological manifestations of the 22q11.2 deletion and proposes guidelines for appropriate screening and management of endocrine disorders in patients with a 22q11.2 deletion. *Genetics in Medicine*, 2001:3(1):19–22.

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Endocrinopathies are common in patients with a 22q11.2 deletion. Abnormal parathyroid function was the first recognized hormonal disturbance in the DiGeorge syndrome, ranging from severe neonatal hypocalcemia to subclinical parathyroid hormone (PTH) insufficiency elicited only with provocative stimuli. As the spectrum of clinical phenotypes that make up the 22q11.2 deletion syndrome has become increasingly better characterized, other hormonal abnormalities, including growth hormone deficiency and hypo- and hyperthyroidism, have been found. Accurate assessment of the prevalence of hormonal disorders in the 22q11.2 is important not only for genetic counseling, but also to provide optimal clinical care to patients. Furthermore, elucidation of the pathophysiology of the hormonal disturbances may provide insights into the molecular mechanisms underlying the 22q11.2 deletion syndrome. This review briefly summarizes our current understanding of the spectrum of endocrinological disorders known to occur in patients with a 22q11.2 deletion, including hypoparathyroidism, growth hormone deficiency, and hypo- and hyperthyroidism, and concludes with suggested guidelines for screening and treatment.

HYPOCALCEMIA

Hypocalcemia is considered one of the cardinal features of the DiGeorge syndrome.[1] Now that the spectrum of the 22q11.2 deletion syndrome has broadened to include the phenotypes of the velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome (CTAFS), and some patients with the Opitz GBBB syndrome, the overall prevalence of hypocalcemia is more difficult to determine. Accurate estimates of the prev-

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alence of hypocalcemia depend not only on the selection criteria used, but also on recognition. Mild or transient hypocalcemia may frequently be missed, so detection requires systematic screening.[2] Patients with the phenotypic characteristics of the DiGeorge anomaly are more likely to have clinical evidence of hypocalcemia or to have calcium levels measured during the course of treatment. When patients with the DiGeorge phenotype are selected, the prevalence of hypocalcemia may be as high as 70%. Bastian found that 13 of 18 patients (72%) with at least two of four features of DiGeorge anomaly (typical facial features, characteristic cardiac lesion, hypocalcemia within the first month of life, and absent thymus) had hypocalcemia.[3] Müller et al., using similar criteria, found hypocalcemia in 11 of 16 patients (69%) studied.[4]

A significantly lower prevalence of hypocalcemia is found when patients are selected on the basis of clinical presentations more consistent with VCFS or CTAFS, in whom calcium levels may not be routinely measured. Motzkin found evidence of transient hypocalcemia in 4 of 18 patients (22%) with VCFS and 22q11.2 deletions,[5] and in another small series of 38 patients, Lipson found 5 with hypocalcemia (13%).[6] In a larger series of 120 patients with VCFS, Goldberg et al. found 20% with hypocalcemia.[7] Matsuoka et al. reported a lower prevalence in a review of 183 patients with CTAFS, in whom 18 (10%) had clinical evidence of hypocalcemia and/or hypoparathyroidism.[8]

More accurate estimations of the prevalence of hypocalcemia may be obtained retrospectively through selection of patients known to have 22q11.2 deletions. We found hypocalcemia in 77 of 158 (49%) patients with a confirmed 22q11.2 deletion.[9] In a very large European cohort, Ryan et al. noted hypocalcemia in 203 of 340 subjects (60%), in whom 39% presented with seizures and 70% were found to have transient hypocalcemia.[10] A summary of the prevalence of hypocalcemia in the 22q11.2 deletion is provided (Table 1).

The hypocalcemia in children with 22q11 deletions is invariably due to hypoparathyroidism, as originally described by DiGeorge in 1965[1] and documented by aplasia or hypoplasia of the parathyroid glands at surgery or autopsy.[11,12] Hypoparathyroid-

Table 1
Prevalence of hypocalcemia by phenotypic characterization

Parameter	Prevalence (%)	Reference
DGS	69–72	3, 4
VCFS	13–22	5–7
CTAFS	10	8
22q11.2 deletion +	49–60	9, 10

DGS, DiGeorge syndrome; VCFS, velocardiofacial syndrome; CTAFS, conotruncal anomaly face syndrome.

ism is most likely to present with symptoms of hypocalcemia–seizures, tremors, or tetany–in the neonatal period. Active transport of calcium from mother to fetus is abruptly interrupted at birth, and calcium intake within the first few days of life is typically insufficient, particularly in sick neonates. This hypocalcemic stress of birth places demands on a reduced parathyroid reserve, and hypocalcemia occurs. In children with severe parathyroid hypoplasia, hypocalcemia is persistent. More commonly, however, hypocalcemia is transient, and as dietary calcium intake increases, the remaining parathyroid activity supplies sufficient PTH to meet metabolic demands. Recurrence of hypoparathyroidism may be precipitated during periods of increased metabolic demand, such as during cardiopulmonary bypass[13] or acute illness,[14] and in adolescence or adulthood[15–17] (and Weinzimer, unpublished observations). Initial presentation of hypoparathyroidism due to a 22q11.2 deletion in adolescence without antecedent transient or neonatal hypoparathyroidism has also been reported.[15–18] The hypocalcemic stress of EDTA infusion has been used to unmask latent hypoparathyroidism in both adults and children.[12,19]

Treatment of severe symptomatic hypocalcemia requires prompt administration of parenteral calcium, 10–15 mg/kg elemental calcium, infused slowly to avoid cardiac dysfunction.[20] Asymptomatic hypocalcemia may be treated with oral calcium supplements, 75–100 mg/kg/day elemental calcium. Maintenance therapy is usually accomplished with 1,25-dihydroxy vitamin D, with or without calcium supplementation. The goal of treatment is not to normalize serum calcium concentrations: in the absence of PTH, urinary losses of calcium remain high, so that patients with hypoparathyroidism are at risk of renal calculi formation. Serum calcium levels should be maintained in the low-normal range (8–9 mg/dL) to minimize hypercalciuria, and patients should be monitored with renal ultrasound examinations at regular intervals for the development of stones.

GROWTH DISORDERS

Growth retardation has been noted in VCFS since 1980, when Young described small stature in 11 of 27 patients (41%),[21] and Shprintzen described height less than the third percentile in 15 of 39 patients (39%).[22] Goldberg et al. postulated that the growth impairment may be related to constitutional delay, as 30% of children but only 10% of adults were short.[7] Ryan noted that 57 of 158 patients with a 22q11.2 deletion were less than the third percentile for height (36%). No-

tably, in that study there were no significant differences in stature related to the presence or absence of cardiac disease.

At the Children's Hospital of Philadelphia, 39 of 95 children (41%) with a 22q11.2 deletion were below the fifth percentile for height, and four children were noted to have extreme short stature (height Z-score less than–2.5 or significantly less than midparental height).[23] All were subsequently found to have growth hormone deficiency: insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels were below age- and gender-related norms, and provocative pituitary testing with arginine, clonidine, and L-dopa demonstrated subnormal maximal growth hormone responses (<10 ng/mL).[24] Of note, none of the four patients had evidence of thyroid disease, and one had hypoparathyroidism. Long-term follow-up has revealed sustained improvements in height and growth velocity in the three children treated with recombinant growth hormone therapy (Figs. 1 and 2).

Brain MRI in two of the four patients revealed anatomic abnormalities, including hypoplastic anterior pituitary and abnormal infundibular insertion with posterior pituitary ectopia. Brain anomalies have been noted previously in VCFS but not within the pituitary gland.[25] Pituitary abnormalities did not correlate with defects in the palate: neither patient with abnormal pituitary anatomy had cleft palate, but velopharyngeal insufficiency was noted in one and short palate was noted in the other. One patient had a normal palate, and the fourth, whose brain MRI was normal, had a frank midline cleft palate. Growth disorders are well-recognized in children with cleft palate; Rudman found that short stature was four times more common and growth hormone deficiency 40 times more common in children with midline clefts, as compared to children without clefts.[26] Our series demonstrated a prevalence of growth hormone deficiency of 4% in patients with a 22q11.2 deletion and 10% of 22q11.2 deletion with short stature.

THYROID DISORDERS

Disorders of the thyroid have been reported sporadically in patients with a 22q11.2 deletion. Driscoll noted hypothyroidism in 1 of 15 (7%) subjects with VCFS,[27] and Wilson reported hypothyroidism in 2 of 44 subjects (5%) with the DiGeorge syndrome.[28] A large European collaborative study found hypothyroidism in 4 of 548 (0.7%) subjects with a 22q11.2 deletion.[10] Goldberg et al. documented primary hypothyroidism (low T4, elevated TSH) in 1 of 120 patients (0.8%) with VCFS,[7] and mild compensated primary hypothyroidism has been seen in an adolescent with a 22q11.2 deletion and VCFS phenotype (Weinzimer, unpublished observation). Congenital hypothyroidism has recently been documented in a newborn with the DiGeorge phenotype and a 22q11.2 deletion.[29]

Congenital abnormalities of the thyroid would not be unexpected in subjects with a 22q11.2 deletion, as both the follicular cells and C cells of the thyroid are at least in part derived from neural crest cells of the fourth and fifth pharyngeal pouches.[30,31] The DiGeorge anomaly is now considered to be a developmental field defect of the cranial neural crest cells of the
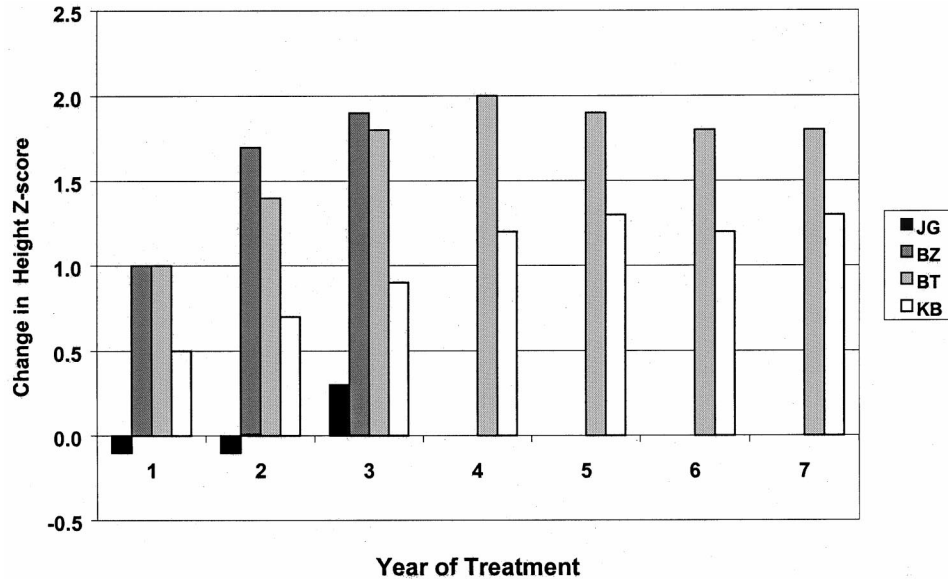
Fig. 1 Sustained improvement in height Z-score in three subjects with a 22q11.2 deletion and growth hormone deficiency treated with growth hormone. An untreated patient with growth hormone deficiency and a 22q11.2 deletion (JG) is shown for comparison.

Fig. 2 Sustained improvement in growth velocity Z-score in three subjects with a 22q11.2 deletion and growth hormone deficiency treated with growth hormone. An untreated patient with growth hormone deficiency and a 22q11.2 deletion (JG) is shown for comparison.
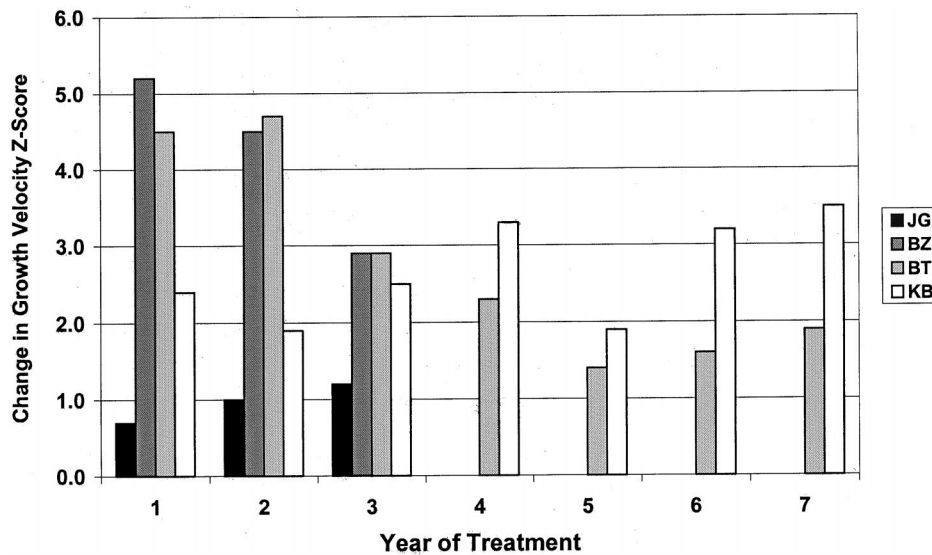
third and fourth pharyngeal pouches.[32] Autopsy reports have revealed multiple abnormalities of the isthmus and/or thyroid lobes in patients with the DiGeorge anomaly.[11,33–36]

Most recently, hyperthyroidism due to Graves disease has been reported in subjects with a 22q11.2 deletion.[37,38] Other autoimmune disorders have also been seen in conjunction with the 22q11.2 deletion, including juvenile rheumatoid arthritis[39–41] and idiopathic thrombocytopenic purpura.[37,42]

HORMONAL EVALUATION AND TREATMENT

Medical evaluation of patients with a 22q11.2 deletion should include particular attention to the three endocrine sys-

tems discussed above. All patients with a 22q11.2 deletion should have serum calcium levels checked periodically; as discussed above, even normal levels do not completely exclude partial hypoparathyroidism. Patients and families should be counseled regarding the symptoms of hypocalcemia: paresthesias, muscle cramps, tremors, and rigidity. New-onset seizures in a patient with a 22q11.2 deletion should prompt an evaluation for hypocalcemia. Both children and adults with a 22q11.2 deletion should be clinically monitored for thyroid abnormalities. As the natural history of thyroid disorders in this population is unknown, baseline screening with T4 and TSH in all patients with the deletion is justified. Subsequent testing should be performed if symptoms of hypo- or hyperthyroid-

ism develop, and standard thyroid replacement or antithyroid therapy should be instituted as indicated.

Growth in children with a 22q11.2 deletion should also be closely monitored. Although short stature is common in children and adults with a 22q11.2 deletion, growth hormone deficiency remains an important, treatable cause of poor growth in this population. Children whose height or growth velocity is less than the fifth percentile for age or who are growing significantly below their genetic potential, should be tested for growth hormone deficiency. If serum insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels are low, insufficient endogenous growth hormone production is likely. Provocative pituitary testing with growth hormone secretagogues should then be performed. We have shown that initiation of growth hormone therapy in growth hormone deficient children with a 22q11.2 deletion is associated with sustained improvements in height and growth velocity.

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