Growth Hormone Deficiency in Patients With a 22q11.2 Deletion: Expanding the Phenotype

ABSTRACT. The list of findings associated with the 22q11.2 deletion is quite long and varies from patient to patient. The hallmark features include: conotruncal cardiac anomalies, palatal defects, thymic aplasia or hypoplasia, T cell abnormalites, mild facial dysmorphia, and learning disabilities. The 22q11.2 deletion has been seen in association with the DiGeorge sequence, velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome, isolated conotruncal cardiac anomalies, and some cases of autosomal dominant Opitz G/BBB syndrome. Short stature has been seen in one to two thirds of children reported in the literature with a diagnosis of VCFS, but growth hormone deficiency (GHD) has not been described in conjunction with this diagnosis. We present 4 patients with a 22q11.2 deletion and short stature who were found to have abnormalities in the growth hormone-insulin-like growth factor I axis. All had growth factors less than −2 SD for age and failed provocative growth hormone testing. Two patients were found to have abnormal pituitary anatomy. In our population, the incidence of GHD in 4 of 95 children with 22q11 deletion is significantly greater than the estimated incidence of GHD in the general population. Children with a 22q11.2 deletion appear to be at a greater risk for pituitary abnormalities. Therefore, those children with the 22q11.2 deletion and short stature or poor growth should be evaluated for GHD, as replacement growth hormone therapy may improve their growth velocity and final height prediction. *Pediatrics* 1998;101:929–932; *velocardiofacial syndrome, DiGeorge sequence, 22q11.2 deletion, growth hormone, deficiency, short stature.*

ABBREVIATIONS. DGS, DiGeorge sequence; VCFS, velocardiofacial syndrome; CTAF, conotruncal anomaly face syndrome; GHD, growth hormone deficiency; SDS, standard deviation score; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein-3; GH, growth hormone; MRI, magnetic resonance imaging; FISH, fluorescence in situ hybridization.

The list of findings associated with the 22q11.2 deletion is quite long and varies from patient to patient. The hallmark features include some combination of the following: conotruncal cardiac anomalies, palatal defects including overt and submucosal cleft palate and/or velopharyngeal incompetence, thymic hypoplasia or aplasia, T cell abnormalities, learning disabilities, and mild facial dysmorphia.

Less commonly occurring features include: cleft lip, hypertelorism, imperforate anus, umbilical or inguinal hernia, hypospadias, cryptorchidism, laryngotracheoesophageal abnormalities,[1] feeding difficulties in infancy,[2] renal abnormalities including Potter sequence or single kidney,[3] and skeletal anomalies such as polydactyly, syndactyly, and butterfly vertebrae.[4] Syndromes presently associated with the 22q11.2 deletion include DiGeorge sequence (DGS),[5,6] velocardiofacial syndrome (VCFS),[7] conotruncal anomaly face syndrome (CTAF),[8] and some patients with autosomal dominant Opitz G/BBB syndrome.[1,9]

The literature on VCFS, which includes patients diagnosed clinically before the advent of microdeletion studies, suggests that short stature is a common feature. The incidence of short stature in VCFS varies from 39% to 67% (Table 1). Goldberg et al[14] suggested that the short stature noted in their patient population was attributable to constitutional delay, because only 10% of adult patients in their series were below their predicted height, as based on comparison to parental heights. To date, there have been no descriptions of growth hormone deficiency (GHD) in children with VCFS or any of the other syndromes associated with the 22q11.2 deletion. At the Children's Hospital of Philadelphia, 39 of 95 of children and 2 of 9 adults with a 22q11.2 deletion were below the 5th percentile for height. Of these, 4 children were noted to have extreme short stature (height below −2.5 standard deviation units [SD]) or heights well below their target height based on midparental values. They were all found to have GHD.

CASE REPORTS

Auxologic data on the 4 patients, including chronological age, skeletal age, target adult height (based on midparental height), height standard deviation score (SDS), and growth velocity SDS, are presented in Table 2. Laboratory investigations, including measurement of the GH-dependent growth factors insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3), maximal growth hormone response to provocative stimuli (GH), thyroxine (T_4), and thyroid-stimulating hormone are also shown in Table 2. All patients were healthy at the time of their evaluations, and none showed clinical or biochemical evidence of poor nutrition or other chronic disease.

Patient 1

This child was a 2.9 kg white girl born at term. An evaluation for failure to thrive in infancy led to the diagnosis of an atrial septal defect, but she continued to grow poorly even after surgical correction. She also had recurrent otitis media, speech delay, and velopharyngeal insufficiency. She was referred at the age of 3 11/12 years for short stature. There was a family history of constitutional delay in her mother, who did not reach menarche until the age of 17 years. Both of her parents were of normal stature, and her target height was 171 cm (+1.2 SD). At the time of her initial evaluation, she was 91.1 cm in height (−2.5 SD) and had an unremarkable physical examination. She was found to have a delayed bone age, low growth factors, and a subnormal GH response to stimulation with arginine and clonidine. Her thyroid function was intact. A brain magnetic resonance imaging (MRI) demonstrated hypoplasia of the anterior pituitary. She was diagnosed with GHD and therapy with GH was initiated at 0.3 mg/kg/wk. Her height and growth velocity SDS improved from −2.5 to −1.8, and −1.6 to +0.7, respectively, after 2 years of GH treatment. Two years later she was referred to clinical genetics for a diagnostic evaluation after her diagnosis of juvenile rheumatoid arthritis-like arthropathy.[17] She was subsequently diagnosed with a 22q11.2 deletion by fluorescent in situ hybridization (FISH) analysis.

Patient 2

This child was a Vietnamese boy born after a term gestation weighing 2.8 kg. His neonatal course was complicated by hypocal-

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TABLE 1. Previous Reports of Short Stature in VCFS

Report	Year	Short Stature (%)	N
Young et al[10]	1980	41	27
Shprintzen et al[11]	1981	39	39
Lipson et al[12]	1991	63	38
Jedele et al[13]	1992	67	15
Goldberg et al[14]	1993	44	75
Motzkin et al[15]	1993	50	18
Seaver et al[16]	1994	67	6

cemic seizures at age 3 weeks. His calcium was 1.77 mmol/L (7.1 mg/dL), phosphorus was 4.17 mmol/L (12.9 mg/dL), and the serum parathyroid hormone was 4.42 pmol/L (42 pg/mL). He was diagnosed with transient hypoparathyroidism that resolved after a short course of calcium therapy. He also had recurrent otitis media, speech delay, and was diagnosed with a short palate. He was referred for poor growth at age 5 7/12 years. There was a history of constitutional delay in both parents: his mother reached menarche at 17 years and his father also reported pubertal delay. Both parents had short stature, and his target height was 161.5 cm (−2.4 SD). At the time of his initial evaluation, his height was 98.8 cm (−3.2 SD) and his physical examination was notable for a flat nasal bridge and slightly posteriorly rotated ears. Biochemical evaluation revealed low growth factors, a subnormal GH response to arginine and clonidine, and normal thyroid function. He was also found to be hypocalcemic, with a serum calcium level of 1.89 mmol/L (7.6 mg/dL) and an undetectable parathyroid hormone level. A brain MRI demonstrated a hypoplastic anterior pituitary gland and abnormal insertion of the infundibular stalk. He was diagnosed with GHD and treated with GH 0.3 mg/kg/wk. His height and growth velocity SDS improved from −3.2 to −1.6, and −3.9 to +2.7, respectively after 2 years on GH therapy. He was started on calcitriol supplementation. Two years later, after the diagnosis of patient 1, a record review crossing GHD with cardiac and or palatal anomalies identified this patient and he was referred to clinical genetics for 22q11.2 deletion studies. He was subsequently found to have the 22q11 deletion by FISH analysis.

Patient 3

This child was a white boy born at 39 weeks weighing 3.5 kg. An evaluation for chronic cough at the age of 2 months led to the discovery of a vascular ring with compression and deviation of the trachea and a ventricular septal defect. The vascular ring was surgically corrected at the age of 4 months. He also had recurrent otitis media and speech delay. He was referred for short stature at 2 11/12 years, at which point he measured 84.4 cm (−2.7 SD). His mother was of normal stature and reached menarche at age 15. His father was of normal height but had two cousins with adult heights less than −2 SD. His target height was 171.5 cm (−0.8 SD). The physical examination was notable for almond-shaped eyes, bulbous nose, thick superior helices, and a normal palate. Endocrinologic testing revealed a delayed bone age, low growth factors, and a subnormal GH response to provocation with arginine and clonidine. His thyroid function was normal. The constellation of dysmorphic features prompted a subsequent referral to the Genetics Division, where he was diagnosed with the 22q11.2 deletion syndrome by FISH analysis. GH therapy had recently been initiated.

Patient 4

This child was a white boy born prematurely at 35 weeks gestation weighing 2.0 kg. He was noted to have dysmorphic features at birth, including cleft palate, midfacial hypoplasia, small anterior fontanel, and ventricular septal defect. He was referred at the age of 10 2/12 years for poor growth and an undescended right testis. He had been previously diagnosed with a 22q11.2 deletion by FISH analysis. There was no family history of short stature or constitutional delay, and his target height was 179 cm (+0.3 SD). On physical examination, his height was 128.2 cm (−1.6 SD). He had a narrow face, malar hypoplasia, protruding ears, and a repaired cleft palate. The phallus was slender and stretched length measured 3 cm. The scrotum was flat. The left testis measured 1 mL, and the right testis was not palpable. He was found to have a delayed bone age, low growth factors, and a subnormal GH response to combined stimulation with arginine and L-dopa. His thyroid function was normal. The findings of small penis and testis and underdeveloped scrotum prompted measurement of serum gonadotropins. The follicle-stimulating hormone level was 1.3 IU/L and leutinizing hormone was undetectable. A brain MRI demonstrated normal pituitary anatomy. The family refused GH therapy.

DISCUSSION

The diagnosis of the 22q11.2 deletion in our patients is well-established (Table 3). Our patients had the typical phenotypic findings of the deletion: palatal defects (in 3 of 4), dysmorphic facial features (in 3 of 4), and cardiac defects (in 3 of 4). In addition, 1 patient previously diagnosed with transient congenital hypoparathyroidism in the neonatal period had evidence of hypoparathyroidism on presentation 5 years later. This may represent recurrence of hypoparathyroidism, which has been reported in the 22q11.2 deletion syndrome,[22] or more likely, persistent subclinical hypoparathyroidism.

The 4 patients in the present series clearly demonstrate abnormalities in their GH axis consistent with GHD. Their actual heights were less than −2 SD for age or −2 SD below their target heights, based upon the gender-corrected midparental heights. Measurements of the GH-dependent growth factors IGF-I and IGFBP-3 were less than −2 SD for age in all 4 children, and all children demonstrated a subnormal rise in GH in provocative testing with clonidine, arginine, or L-dopa. Although pharmacologic provocative testing is the currently accepted standard for diagnosing GHD, auxologic criteria and measurement of IGF-I and IGFBP-3 may actually be more sensitive and specific.[20] The growth velocities, growth factor levels, and response to pharmacologic stimuli in these 4 patients all clearly document GHD.

Although all 4 patients had abnormalities in GH secretion, none had evidence of thyroid-stimulating hormone or adrenocorticotropic hormone deficiency,

TABLE 2. Auxologic and Biochemical Data Obtained at the Time of Evaluation for Short Stature

Patient	Age	Skeletal Age	Midparental Height SDS	Actual Height SDS	Growth Velocity SDS	IGF-I* SDS (nmol/L)	IGFBP-3* SDS (nmol/L)	GH† (μg/L)	T_4* (nmol/L)	TSH (mU/L)
1	5.4	3.5	+1.2	−2.5	−1.6	6.28 (−2.3)	26.7 (−2.7)	9.3‡	104	1.9
2	5.6	5.0	−2.4	−3.2	−3.9	1.57 (−2.8)	23.3 (−2.8)	7.1‡	85	2.3
3	4.1	3.0	−0.8	−3.0	−1.7	5.23 (−2.2)	36.7 (−2.2)	9.3‡	116	0.9
4	10.7	9.5	+0.3	−1.7	−1.2	15.03 (−2.4)	56.7 (−2.2)	8.8	112	1.1

* SI unit conversion: multiply IGF-I by 7.649 for ng/mL; multiply IGFBP-3 by 0.03 for mg/L; multiply T_4 by 0.0777 for μg/dL.
† Maximum GH level obtained after provocative testing with arginine (0.5 g/kg) and clonidine (0.1 mg/m²)‡ or with arginine (0.5 g/kg) and L-dopa (500 mg/1.73 m²)§.

TABLE 3. Phenotypic Findings in Four Patients With 22q11.2 Deletion Syndrome and GHD

Patient	Facial Dysmorphia	Palate	Cardiac	Other	MRI
1	None	VPI	ASD	JRA	Hypoplastic anterior pituitary
2	Flat nasal bridge, posteriorly rotated ears	Short	Normal	Hypoparathyroidism	Hypoplastic anterior pituitary, abnormal infundibular insertion
3	Bulbous nose, thick superior helices	Normal	Vascular ring VSD	—	—
4	Midfacial hypoplasia, protruding ears	Cleft	VSD	Micropenis, cryptorchidism	Normal

by clinical or biochemical criteria. Patient 4, who presented with an undescended testis and micropenis, had an undetectable LH level, as measured by an ultrasensitive immunochemiluminometric assay.[21] Although low-serum gonadotropins cannot differentiate a normal prepubertal child from one with hypogonadotropic hypogonadism, the physical features and LH level do suggest hypogonadotropic hypogonadism.

It has been hypothesized that deletions in the 22q11.2 locus may influence the development of structures derived from the neural crest, including the 3rd and 4th pharyngeal pouches, and may affect the development of the oral ectoderm into the anterior pituitary and palate. Abnormalities of the pituitary were documented in 2 of the 3 children in whom MRIs were obtained: anterior pituitary hypoplasia and abnormal insertion of the infundibular stalk. The degree of palatal involvement does not predict the extent of the anatomic or physiologic pituitary dysfunction. Patients 1 and 2 had milder palatal defects (velopharyngeal insufficiency and shortened palate) and isolated GHD but frankly abnormal pituitary glands by MRI, while patient 4 had an overt cleft and evidence of hypogonadotropism but normal pituitary anatomy.

The incidence of GHD in the general population is approximately 1:4000–10 000, but has been noted to be higher in children with cleft palate. In a study of 33 children with cleft lip and/or palate, Laron et al[18] found growth retardation (height <3%, delayed bone age) in 3. Of the 2 patients who underwent further evaluation with arginine and insulin-induced hypoglycemia, both were found to be GH-deficient. Thyroid and adrenal functions were normal in both patients, and gonadotropins were present in 1 child who was tested. They postulated that in some patients with clefts, the normal hypothalamic-pituitary pathways were disrupted during the embryologic development of the facial structures. Rudman et al[19] investigated a larger group including 200 children with cleft lip or palate and compared them with normally growing children and short children (height <3%) without facial clefts. Using arginine and insulin-induced hypoglycemia, they found impairments in GH secretion in 4% of all children with clefts and 32% of the short children with clefts. They concluded that short stature is 4 times more prevalent, and GHD is 40 times more prevalent, in children with clefts compared with those without clefts. They suggested that because of the spatial and temporal proximity of the development of the palate and adenohypophysis, both processes could be disturbed by the same teratogenic factors. Both of these older studies may have included patients with 22q11 deletion. In the Children's Hospital of Philadelphia series, GHD was present in 4% of all 22q11 patients and 10% of 22q11 patients with short stature.

CONCLUSION

Children with a 22q11.2 deletion may be at increased risk for pituitary deficiencies. The short stature that has previously been reported as part of the VCFS may in fact be a result of impairments in GH secretion, and as such, may be amenable to replacement GH therapy. Although GHD is a well-recognized complication of cleft palate, abnormalities of the GH-IGF-I axis may be present in 22q11.2 patients even in the absence of true clefting or overt pituitary abnormality. Evaluation of the GH axis, including serial determination of height and growth velocity, and measurement of growth factors and provocative GH levels, is therefore indicated in short children with the 22q11.2 deletion.

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