

The Spectrum of Growth Abnormalities in Children with 18q Deletions*

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ABSTRACT

The objective of this study was to assess the spectrum of growth abnormalities in children with 18q deletions. The growth axis of 50 individuals with a cytogenetically and molecularly confirmed 18q deletion was investigated by determining height, growth velocity, insulin-like growth factor I (IGF-I), IGF-binding protein-3, bone maturation, and response to pituitary stimulants of GH.

Children with 18q deletions are short; 64% have a height more than -2 SD below the mean. Affected children also grow slowly; 68% have a growth velocity more than -1 SD below the mean. Half of the

individuals have delayed bone maturation. Growth factors are skewed downward; 72% of the IGF-I values and 83% of the IGF-binding protein-3 values are below the mean for chronological age. Similarly, 72% of the children had a reduced or absent response to either of the GH stimulants, arginine and clonidine. In the total group of 50 children only 2 were normal for all parameters evaluated.

Short stature and poor growth are common features of individuals with 18q deletions. GH deficiency is common in this cohort of patients and probably plays a role in the short stature seen in many of the affected individuals. (*J Clin Endocrinol Metab* 85: 4450–4454, 2000)

A DELETION OF a segment of the long arm of the 18th chromosome (18q) is one of the most common of the human segmental aneusomies, with an estimated prevalence of about 1 in 40,000 live births (1). Phenotypic findings of this aneusomy include short stature and slow growth, as well as hearing loss, hypotonia, developmental delay, proximal thumbs, and delayed myelination (2–7). There are case reports (2–6) of children with 18q deletions and GH deficiency (GHD); however, there has been no systematic search for growth abnormalities and GHD in a large cohort. In this study we evaluated growth and growth-related parameters in 50 individuals with cytogenetically and molecularly confirmed deletions involving only chromosome 18q. This study is part of a large, longitudinal, multidisciplinary project to fully characterize the phenotypes associated with 18q deletions and to correlate the phenotype with detailed molecular genotypes (7–9).

Materials and Methods

Individuals with 18q deletions were referred by the Chromosome 18 Registry and Research Society, geneticists, and pediatric endocrinologists. The study coordinator and family collaborated to recover comprehensive medical records for each child. Requirements for participation included the absence of translocation or mosaicism, both parents with normal karyotype, and willingness to come to this center for evaluation. If the available cytogenetic report was less than 550 band level resolution, the 18q diagnosis was confirmed in our laboratory. Because of a genotype-phenotype mapping project underway in this center, all

participants had detailed molecular analysis confirming the deletion of 18q (8, 9).

Consent for study participation was obtained from the parent or guardian, and when appropriate, assent was obtained from children more than 7 yr of age. The institutional review board of the University of Texas Health Science Center (San Antonio, TX) approved all studies. They were also reviewed and approved by the research and development committee of the Audie Murphy V.A. Hospital and the advisory committee of the General Clinical Research Center.

For children 3 yr or older, height was determined using a wall-mounted stadiometer, and height z-score (HTZ) was calculated by a computer program designed for this purpose (Growth Base III, Eli Lilly & Co., Indianapolis, IN). For children less than 3 yr old, length was determined using a board-mounted stadiometer, and HTZ was calculated based on normative data (5, 10). Growth velocity was determined by subtracting a height (length) obtained at least 3 months before the visit from the height (length) obtained at the time of visit. To assure that the velocity calculated for the months preceding the visit to this center were consistent with previous velocities, the velocity was also compared with calculated velocities from the historical height record. For children 3 yr or older, growth velocity z-score (GVZ) was calculated by Growth Base III (Eli Lilly & Co.). For children less than 3 yr old, GVZ was calculated in a manner similar to that described for calculating HTZ in this age group (5, 10). An x-ray of the left hand and wrist was obtained at the initial visit for bone age (BA) determination (11). A BA that was less than -2 SD for age was considered delayed.

The standard protocol included the measurement of insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3), L - T_4 , and TSH. If the TSH was elevated, the child was treated with L - T_4 , and the GH-related studies were repeated when T_4 was in the mid-normal range and TSH was normal. Of the total group of children, 2 (4%) were receiving L - T_4 replacement at the time of testing. The IGF-I z-score (IGF-IZ) and IGFBP-3 z-score (BP3Z) were calculated using an algorithm and normative data provided by Genentech, Inc. (South San Francisco, CA). Due to the inconsistent association of BA delay and GHD (12), all data are normalized to chronological age. For GH provocative testing, children were admitted to the General Clinical Research Center on the preceding evening. After pretreatment of the insertion site with an anesthetic cream (EMLA cream, AstraZeneca, Wilmington, DE), a peripheral intermittent iv device was placed in an arm vein at least 30 min before the start of the test. Each test was begun between 0800–0900 h after an overnight fast. GH production was evaluated using one or more provocative stimuli: clonidine hydrochloride (50 mg if <15 kg, 100 mg for 15–45 kg,

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150 mg for >45 kg), arginine (0.5 g/kg), and sermorelin acetate (1 µg/kg; Geref, Serono, Milan, Italy) (13). These stimulants were chosen because they permit an exploration of the hypothalamic-pituitary axis; clonidine stimulates GHRH, whereas arginine inhibits somatostatin. Sermorelin acetate is a direct stimulant of GH release. Not all studies were performed on all individuals. Sex hormone priming was not done. Nichols Institute Diagnostics (San Juan Capistrano, CA) performed all hormonal assays. GH was measured by polyclonal RIA.

Case reports

Four children are presented in Table 1 who demonstrate the spectrum of growth abnormalities associated with 18q deletions. Some affected children, such as patient 8, have an unequivocally normal growth axis, as defined by normal height and growth velocity, normal growth factors, and normal responses to GH stimulation testing. Others, such as patient 46, have classical GHD, delineated by height less than -2 sd, growth velocity less than -1 sd, low growth factor levels, and failure of GH response to two provocative tests. However, the preponderance of affected children, as illustrated by patients 4 and 57, fall somewhere between these two extremes.

Results

Fifty individuals with 18q deletions have been evaluated, including 34 females and 16 males, ranging in age from 4–264 months (mean ± sd, 68 ± 54 months). Forty-five (90%) were prepubertal, 2 (4%) were pubertal (1 Tanner stage 2 for pubic hair and breast development, 1 Tanner stage 4 for pubic hair and breast development), and 3 (6%) were postpubertal (Tanner stage 5 for pubic hair and breast development). Forty-four (88%) were of northern European heritage, 4 (8%) were Hispanic, 1 (2%) was African American, and 1 (2%) was of mixed heritage. The children were from 27 states in the United States and 3 other countries (Canada, South Africa, and Italy).

Table 2 summarizes the auxological and growth factor evaluation performed on the group, showing mean, median, and range for these parameters and providing the overall distribution of the group. Children with 18q deletions are short compared with peers. The mean HTZ is -2.24 ± 1.35 . Of the group, 32 (64%) had heights less than -2 sd. Fur-

thermore, only 3 (6%) children had heights greater than 0 sd. The parents were of average height (paternal HTZ, 0.3 ± 1.2 ; maternal HTZ, 0.1 ± 1.1). Mean birth weight was 2.83 kg, with a range of 1.6–3.8 kg. The upper to lower segment ratio was increased (5). The children were of appropriate weight for height. The mature heights of 3 postpubertal females included in this report were 151, 124, and 153 cm. Four additional adult females were seen at this center, but did not undergo growth axis evaluations; their heights were 146.5, 150.3, 152.4, and 151.9 cm. The group mean height of all 7 young women was 147 ± 9.7 cm (-3.1 sd for adult females). None of these 7 women had received GH treatment.

Children with 18q deletions grow poorly compared with peers. The group GVZ is -1.03 ± 1.37 . Twenty-five (50%) had a velocity less than -2 sd below the mean, and an additional 9 (18%) had velocities between -1 and -2 sd. Only 3 (6%) had growth velocities greater than 0 sd. Although many of the children had multiple medical problems, none had conditions such as cyanotic heart disease or malabsorption that could potentially hinder normal growth. HTZ and GVZ were strongly correlated ($P = 0.002$, Pearson correlation coefficient).

Half of the children exhibited bone maturational delay. Less than 5% of the parents and siblings had a history of pubertal delay. Of the three postpubertal females presented here, the onset of menstruation was only slightly delayed (mean age, 13.8 ± 0.9 yr). The results of Student's *t* test analyses indicate that children with delayed bone maturation are significantly shorter than those without delayed bone maturation (HTZ, -2.7 vs. -1.7 ; $P = 0.003$). Although the mean growth velocity is slower in those with bone maturational delay, this does not reach statistical significance ($P = 0.54$).

Children with 18q deletions often have low growth factors and reduced response to GH stimulation testing. The group IGF-IZ was -0.99 ± 1.37 . Of the group, 70% of the IGF-I values and 83% of the IGFBP-3 values were below the mean

TABLE 1. Case histories: spectrum from normal growth to GH deficiency in children with 18q deletions

| | | | | |
|------------------------------------|----------------------------|-----------------------|-----------------------|-----------------------|
| Patient no. | 8 | 4 | 57 | 46 |
| Age at visit 1 (months) | 102 | 103 | 24 | 33 |
| Sex | M | F | F | M |
| Ht (cm)/z | 130.9/-0.1 | 127/-0.6 | 72/-3.8 | 82.4/-2.5 |
| Wt (kg)/z | 26/-1.1 | 27/0.2 | 7.1/-4.7 | 9.4/-3.9 |
| Velocity (cm/yr)/z | 7.5/0.4 | 6.0/0.4 | 5.1/-2.2 | 4.8/-2.5 |
| Common phenotypic features | | | | |
| Hearing | Normal | Atretic canals | Normal | Reduced |
| Skeletal | Proximal thumbs | Spinal abnormalities | Abnormal 2nd toe | Proximal thumbs |
| Other | Mild autism | Myopia | Atrial septal defect | Vertical talus |
| 18q cytogenetic breakpoint | 46,XY,del(18) (q21.3 Ψq23) | 46,XX,del(18) (q21.3) | 46,XX,del(18) (q21.3) | 46,XY,del(18) (q21.2) |
| T ₄ (pmol/L)/TSH (mU/L) | 91/0.7 | 113/NA | 107/1.94 | 84/6.5 |
| IGF-I (µg/L)/IGF-IZ | 154/-0.67 | 157/-1.33 | 43/-0.66 | 27/-1.34 |
| IGFBP-3 (µg/L)/BP-3Z | 2.7/0.63 | 2.1/-0.50 | 1.1/-1.80 | 0.8/-2.67 |
| AMXGH (µg/L) | 15.4 | 2.6 | 20.4 | 5.1 |
| CMXGH (µg/L) | 5.0 | N.D. | 15 | 1.7 |
| Growth parameter summary | | | | |
| Growth | Normal | Normal | Slow | Slow |
| IGF-I/IGFBP-3 | Normal | Normal | Abnormal | Abnormal |
| GH response | Normal | Abnormal | Normal | Abnormal |
| Follow-up information | | | | |
| Age | 127 months | 152 months | 38 months | 65 months |
| HTZ | 0.8 | -2.8 | -4.4 | -1.5 |
| Treatment | None | None | None | On GH Rx. |

TABLE 2. Summary of auxology and test results on children with 18q deletions

| | n | Mean \pm SD | Median | Range | % of patients | | | |
|----------|----|------------------|--------|------------|---------------|---------------|----------------|---------------|
| | | | | | >0 SD | 0 to -1 SD | -1 to -2 SD | >-2 SD |
| HTZ | 50 | -2.24 \pm 1.35 | -2.40 | -5.21-0.80 | 6 | 14 | 18 | 64 |
| GVZ | 50 | -1.03 \pm 1.27 | -1.20 | -3.02-1.71 | 6 | 26 | 18 | 50 |
| IGF-IZ | 44 | -0.99 \pm 1.37 | -1.25 | -3.39-1.83 | 28 | 20 | 27 | 15 |
| BP3Z | 47 | -0.70 \pm 0.93 | -0.56 | -2.68-1.77 | 17 | 49 | 26 | 9 |
| | | | | | >10 ng/mL | 7-10 ng/mL | | <7 ng/mL |
| AMXGH | 25 | 8.95 \pm 7.16 | 5.90 | 1.2-30.1 | 28 | 16 | | 56 |
| CMXGH | 42 | 9.46 \pm 7.25 | 8.10 | 1.1-31.9 | 28 | 36 | | 36 |
| Bone age | 46 | | | | | Normal 50 | | Delayed 50 |

TABLE 3. Comparison of children with 18q deletions to other causes of short stature

| Diagnosis | 18q-deletions | Turner syndrome | Idiopathic short stature | Organic GHD | Idiopathic GHD |
|-----------------------|----------------|-----------------|--------------------------|----------------|----------------|
| No. of patients | 50 | 2148 | 3027 | 2762 | 8983 |
| Baseline age (yr) | 5.8 \pm 4.6 | 9.1 \pm 3.7 | 10.1 \pm 3.6 | 8.5 \pm 4.8 | 9.4 \pm 4.2 |
| Baseline HTZ | -2.2 \pm 1.4 | -3.0 \pm 0.9 | -2.8 \pm 0.9 | -2.4 \pm 1.5 | -2.7 \pm 1.1 |
| Maternal HTZ | 0.1 \pm 1.1 | -0.3 \pm 1.2 | -0.9 \pm 1.2 | -0.3 \pm 1.3 | -0.7 \pm 1.2 |
| Paternal HTZ | 0.3 \pm 1.2 | -0.0 \pm 1.2 | -0.6 \pm 1.2 | -0.1 \pm 1.3 | -0.4 \pm 1.3 |
| Baseline rate (cm/yr) | 4.7 \pm 2.4 | 4.0 \pm 2.3 | 4.4 \pm 2.1 | 4.3 \pm 3.3 | 4.5 \pm 2.8 |
| BA/chronological age | 0.75 | 0.86 | 0.80 | 0.86 | 0.81 |
| Maximum GH (ng/mL) | 9.6 \pm 7.4 | 10.4 \pm 8.8 | 14.0 \pm 9.2 | 2.7 \pm 5.4 | 5.6 \pm 2.7 |

for chronological age. IGF-I and IGFBP-3 correlated well with height ($P < 0.01$ and $P < 0.001$, respectively, based on Pearson correlation coefficients), but not with growth velocity, bone age delay, or response to stimulation testing with clonidine or arginine. There is a wide spectrum of responses to GH stimulation testing with both arginine (GH peaks from 1.2-30.1 $\mu\text{g/L}$) and clonidine (GH peaks from 1.1-31.9 $\mu\text{g/L}$). In response to arginine, 56% had a peak GH value below 7 ng/mL. In response to clonidine, 36% had a peak GH value below 7 $\mu\text{g/L}$, and another 36% had peaks between 7 and 10 $\mu\text{g/L}$. Four of five children tested with sermorelin gave normal responses (mean, 37; range, 9-58 $\mu\text{g/L}$). The peak GH response with either arginine or clonidine did not correlate with the HTZ, GVZ, IGF-IZ, or BP3Z. The maximum GH response to arginine was more likely to be low in children with delayed bone ages ($P = 0.03$, by Kruskal-Wallis test), but this correlation was not seen with the maximum GH response to clonidine.

In summary, abnormalities of growth, growth-related factors, and GH are common in children with 18q deletions. Only two individuals (4%) were unequivocally normal for all parameters evaluated. Most children with 18q deletions have abnormalities of the growth axis, and many of the children are GH deficient using classical criteria.

Discussion

Four groups of children derived from the National Cooperative Growth Study (14-16) provide useful comparisons in evaluating children with 18q deletions, as summarized in Table 3. At the time of initial evaluation, the mean age of children with 18q deletions was less than those of the other four groups. There are several possible reasons for this. Children with 18q deletions have nonstatural medical problems

that increase their exposure to health care providers; therefore, their short stature may be noted at an earlier age. This possibility is supported by the observation that children with 18q deletions are not as far behind their peers in linear growth at the time of initial evaluation as children in the other groups. Most of our patients were referred within the past 5 yr. During this period, there has been increased public awareness regarding the GH treatment of short stature, possibly leading to earlier referral for evaluation. Over the last several years, parents of children with genetic syndromes have sought out support groups and additional information via the internet, perhaps leading to earlier referral to appropriate resources. Because of greater parental heights in the 18q- syndrome group, parents may be more aware of their child's short stature and poor growth.

Baseline growth velocity was slightly higher in children with 18q deletions compared with that in the other groups. This may reflect the relative youth of the children in our dataset. The optimal way to compare the growth velocities of these populations is to compare GVZs. The published data on the other conditions do not provide baseline GVZ. However, the mean baseline growth velocity of the 18q- syndrome group (mean age, 5.8 yr) and the Turner syndrome group (mean age, 9.1 yr) are both -1.6 SD below the mean for age.

The bone maturation of the children with 18q- deletions was about 75% of normal, with wide variability. Although directly comparable results are not available for the other four groups, the ratio of mean BA to chronological age is within the same range as that in the 18q deletion group.

Maximum stimulated GH in children with 18q deletions is similar to that in Turner syndrome, lower than that in idiopathic short stature, and somewhat higher than that in idiopathic and organic GHD. Of the individuals with 18q de-

letions, only four had structural abnormalities of the pituitary by magnetic resonance imaging (two small for age, one with small cyst, and one with absent pituitary bright spot). Many also have other evidence of hypothalamic dysfunction, including abnormal TSH response to provocative testing with TRH and elevated basal PRL (17, 18).

Abnormal growth is a common feature of numerous aneuploidies. The mechanism(s) that results in poor growth and short adult height has not been elucidated. It is probable that growth failure is a final common result of numerous different mechanisms involving decreased GH production, reduced tissue response to GH, or both. In any individual slow growth may reflect a single factor or combination of factors. For example, GH production is normal in children with cyanotic congenital heart disease, whereas growth is poor (19). Correction of the heart disease improves growth substantially, and many of the children achieve normal adult stature. Children with Down syndrome often have cyanotic congenital heart disease. Correction of the heart disease also improves growth, although the children do not achieve normal adult heights (20). In both instances, there is reduced tissue responsiveness that is corrected by surgery; however, in the child with Down syndrome, there are additional factors contributing to the poor growth.

As the understanding of molecular mechanisms increases, it is increasingly evident that growth failure in each aneuploidy is unique. Poor growth may be due to the loss of one copy of the gene for a factor directly involved in the GH pathway. However, no genes known to be important in growth have yet been identified on 18q. We have identified a region on 18q that is lost in all individuals with GHD (21). This is a region of approximately 2 Mb and is therefore anticipated to contain about 60 genes, only 2 of which have been identified to date. One of these genes, the galanin receptor type I (GALR1), is an excellent candidate gene for GHD due to its hypothalamic involvement in GH regulation (22).

The only aneuploidies in which sizable cohorts of children have undergone growth axis evaluation are Down (20) and Turner (14) syndromes. Although both of these aneuploidies are more genotypically homogeneous than those with 18q deletions, a similar broad spectrum of growth abnormalities has been demonstrated.

The consequences of abnormalities of the growth axis and the benefits of treatment may be highly variable, depending on deleted and duplicated genes. For example, clear benefit from treatment has been demonstrated in Turner syndrome (14), whereas minimal benefit has been seen in Down syndrome (23). Independent of aneuploidies, a wide range of neurocognitive defects have been associated with short stature and GHD (24), and some studies have suggested substantial benefit from GH treatment (25). Evidence continues to accumulate that GH has a host of nonstatural benefits, ranging from improved muscle strength to increased sense of well-being to enhanced lean muscle mass to augmented lymphocyte function (26–28). General benefits of GH therapy that are not specifically related to molecular defects could also prove beneficial in children with 18q deletions. For example, improvements in muscle tone may be more appar-

ent and clinically significant in a population that has poor tone before the initiation of therapy (28).

There is increasing evidence that GH and IGF-I have access to specific areas of the brain, including the hypothalamus, choroid plexus, hippocampus, amygdala, and putamen (29–31). The precise function and mechanism of action in each location have not been elucidated, although there is speculation that GH may have effects on cognitive functions, memory, motivation, and attention. Investigations in children with genetic defects, such as 18q deletions, provide the possibility of uncovering additional roles for GH and IGFs in the central nervous system. Ultimately, this may lead to the discovery of novel mechanisms and new genes that not only enhance understanding of the disorder, but also suggest potential treatment approaches.

In conclusion, children with 18q deletions have a high frequency of growth failure and GHD and merit a careful, thoughtful evaluation of their growth. The beneficial effect of GH treatment for those children with 18q deletions and GHD is currently an area of active investigation. Preliminary results appear highly positive (32).

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