

The Spectrum of Thyroid Abnormalities in Individuals with 18q Deletions

Rebecca L. Schaub, Daniel E. Hale, Susan R. Rose, Robin J. Leach, and Jannine D. Cody

Departments of Pediatrics (R.L.S., D.E.H., J.D.C.) and Cellular and Structural Biology (R.J.L.), University of Texas Health Science Center, San Antonio, Texas 78229; and Division of Endocrinology, Cincinnati's Children's Hospital Medical Center and University of Cincinnati (S.R.R.), Cincinnati, Ohio 45229

Chromosome 18q deletions (18q–) are survivable autosomal deletions, having an estimated incidence of one in 40,000 live births. Our long-term goals were to 1) comprehensively define the endocrine phenotype, 2) determine the natural history, and 3) identify key genes leading to particular phenotypes. This report specifically emphasizes the thyroid phenotype. Medical record review and comprehensive clinical assessment(s) were performed on 120 individuals with 18q– at the Chromosome 18 Clinical Research Center, the largest group of individuals with 18q– ever assembled. Affected subjects ranged in age from 6 wk to 32 yr at initial assessment. Due to case reports of thyroid dysfunction in 18q deletions and the

well-established association between hypothyroidism and aneusomies, we undertook thyroid testing in all individuals and completed TRH studies on 50 of them. Our studies demonstrated that 12% had hypothyroidism, and the results were consistent with primary thyroidal dysfunction. Furthermore, two individuals progressed from normal to abnormal over the course of 2 yr. Based on these studies, it appears that, as is the case in other aneusomies, annual thyroid testing, using TSH as a primary screening tool, is indicated. The mechanism of the hypothyroidism is not yet known, and the genetic basis has not been delineated. (*J Clin Endocrinol Metab* 90: 2259–2263, 2005)

DELETIONS OF THE long arm of chromosome 18 (18q–) are among the most common of human aneusomies, estimated to occur in one of every 40,000 births (1). Common features of affected individuals include proximal thumbs, atretic or stenotic auditory canals, intellectual disability, delayed myelination of the brain, and GH deficiency (2, 3). The phenotypic spectrum ranges widely, from severely impaired, medically fragile children to relatively healthy children with normal intelligence (4). The severity of the phenotype is correlated not only with the size of the deletion, but also with the location of the deletion on the chromosome (5). We have a long-standing interest in the clinical manifestations of 18q deletions. The study reported here is part of a longitudinal comprehensive clinical and molecular assessment of individuals with chromosome 18 abnormalities.

Growth failure was recognized early as a significant clinical manifestation of 18q– (6). However, only recently was GH deficiency identified as a common cause of poor growth in these individuals (7). The majority (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 affected children have delayed bone maturation. Growth factors are usually in the low normal range; 72% of the IGF values and 83% of the IGF-binding protein-3 values are below the mean for chronological age. The majority (72%) of the children had a reduced or absent GH response to arginine, clonidine, or both (8).

As part of our comprehensive assessment of children with

18q deletions, we measured thyroid function tests and performed TRH stimulation tests on 50 subjects. These studies were performed because of the known effect of thyroid hormone on growth and the relatively high prevalence of thyroid dysfunction in other human constitutional aneusomies. For example, Hashimoto's thyroiditis has been documented in individuals with Down's syndrome (9, 10) and Turner syndrome (11, 12). Graves' disease has been associated with DiGeorge syndrome (13, 14). The results reported in this paper represent the largest survey of thyroid abnormalities ever undertaken in individuals with 18q deletions.

Subjects and Methods

Study participants were recruited from the Chromosome 18 Registry and Research Society or were referred to our study by their local physicians. Inclusion criteria for the protocol were a *de novo* deletion of 18q (confirmed by a cytogenetics report at or above the 550-band level) and willingness to travel to our center for evaluation. Subjects who had begun GH treatment before study enrollment were excluded from this analysis.

All subjects and their parents participated in the informed consent process, which was appropriately documented. When appropriate, assent was obtained from children older than 7 yr of age. All studies were reviewed and approved by the institutional review board of University of Texas Health Science Center, the research and development committee of the Audie L. Murphy Veterans Affairs Hospital, and the advisory committee of the General Clinical Research Center.

Height, weight, temperature, and blood pressure (BP) were measured upon patient admission to the General Clinical Research Center. For children 3 yr or older, height was determined using a wall-mounted stadiometer. For children less than 3 yr old, length was measured using a board-mounted stadiometer. Height z-score was calculated based on normative data (www.cdc.gov/growthcharts). Normative data were also used for calculating weight z-scores and body mass index z-scores.

Control data for thyroid function tests were from 96 normal children (40 girls and 56 boys), 76 of whom provided normal data for response to TRH (15, 16). Controls were healthy children and adolescents re-

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Abbreviation: BP, Blood pressure.

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cruited to be normal volunteers. Age ranged from 5–18 yr; height was between the 5th and 95th percentile; weights were normal for height.

Serial TSH levels were measured in response to TRH administration [Thyrel TRH (protirelin), Ferring, Tarrytown, NY]. Subjects fasted a minimum of 2 h before the start of the test. Thirty minutes after topical application of an anesthetic cream (EMLA cream, AstraZeneca, Wilmington, DE), a heparin lock was placed in an arm vein. The heparin lock was flushed with 0.6 ml (10 U heparin/ml; withdrawal discard volume, 0.5 ml) or was infused with 0.45 normal saline at 10 cc/h. After the baseline TSH was determined, a TRH dose of 7 $\mu\text{g}/\text{kg}$ (200 μg maximum) was injected slowly, and blood samples were drawn at 30, 60, 90, and 120 min. Total T_4 was measured in all subjects.

Nichols Institute Diagnostics (San Juan Capistrano, CA) performed all hormonal assays. Total T_4 levels were determined by RIA with a sensitivity of 1 $\mu\text{g}/\text{dl}$ (0.01 mg/liter). TSH levels were measured by immunochemiluminometric assay with a sensitivity of 0.01 mU/liter.

Statistical analyses

Two-tailed z-tests were used to compare the average values from the participants with 18q– to the average values in the control group. Averages were calculated for the following parameters: basal TSH, peak TSH, peak/basal ratio, peak time, and total T_4 . The 18q– and control groups were also subdivided by age and gender for comparison and statistical analysis.

Results

Selected case reports

Five cases are presented to illustrate the spectrum of thyroid findings. These cases are from the endocrinology module of our comprehensive phenotype/genotype assessment of individuals with 18q deletions. Each subject upon study enrollment is assigned a number when medical records and blood samples are submitted for DNA analysis, and that study number is permanent regardless of any future enrollment in our numerous substudies (*e.g.* magnetic resonance imaging, hearing, endocrinology, *etc.*). This number is used in this and all publications.

Normal thyroid status

Subject 51 was evaluated in our center at the age of 7 yr, 2 months. Height was 114.3 cm (10th percentile), and weight was 23 kg (50th percentile). Vital signs were within normal limits. Her medical history was unremarkable, and her intelligence quotient was 86. This child was later determined to have a small terminal deletion of 18q23. All thyroid function tests were normal. Total T_4 was 12.9 $\mu\text{g}/\text{dl}$. The TSH level at baseline was 1.9 mU/liter, rose to a peak of 29 mU/liter at 30 min, and dropped to 9.8 mU/liter by 120 min.

Hypothyroidism as an adult

Subject 71M was a 32-yr-old G₂P₁ female. Height was 152.4 cm (<5th percentile), weight was 62.4 kg (75th percentile), and body mass index was 26.88 kg/m². BP was 128/77 mm Hg. Proximal thumbs were observed on the dysmorphology exam. Her medical history was significant for surgical repair of auditory canal atresia, bipolar disorder, and reflex sympathetic dystrophy. She had an intelligence quotient score in the normal range (106). Her total T_4 level was normal at 7.5 $\mu\text{g}/\text{dl}$; however, the TSH level at baseline was high at 7.5 mU/liter, rising to an elevated peak of 75.7 mU/liter at 30 min. At 120 min, the TSH level had returned approximately halfway to baseline (36.6 mU/liter). Based on these results,

L-T₄ was initiated at a dose of 0.05 mg daily and was adjusted appropriately to achieve a normal TSH.

Acquired hypothyroidism as a child

Subject 69 was evaluated twice at our center. His first visit was at age 6 yr. Height was 104 cm (less than fifth percentile), and weight was 15.4 kg (less than fifth percentile). BP was 92/62 mm Hg. Physical exam was otherwise unremarkable. Past medical history was significant for surgical repair of a left clubfoot and bilateral repair of external auditory canal atresia. Thyroid function tests were normal. Total T_4 was 7.1 $\mu\text{g}/\text{dl}$. The TSH level was 3.49 mU/liter at baseline and rose to a peak of 27.2 mU/liter at 30 min. On his second visit at age 8 yr, 5 months, his height and weight were 119 cm (fifth percentile) and 18.9 kg (fifth percentile). BP was 93/45 mm Hg. His T_4 level was still in the normal range at 5.8 $\mu\text{g}/\text{dl}$; however, his basal TSH was high at 16.3 mU/liter, with a very elevated peak of 96.4 mU/liter at 30 min. L-T₄ treatment was initiated at 0.0375 mg daily.

Progression of thyroid disease in a child

Subject 57 was also evaluated twice at our center. The initial visit was at age 3 yr, 2 months. Height was 78.1 cm (less than fifth percentile), weight was 9.1 kg (less than fifth percentile), BP was 103/74 mm Hg. Her medical history was significant for an atrial septal defect and low IgA levels. Total T_4 was normal at 9.5 $\mu\text{g}/\text{dl}$. The baseline TSH value was slightly above normal at 7.5 mU/liter, with a peak of 60.8 mU/liter after TRH. L-T₄ was initiated at 0.025 mg daily. The subject returned to our center at age 6 yr. Height and weight were significantly below the fifth percentile, at 92.7 cm and 13.6 kg, respectively. BP was 95/36 mm Hg. All thyroid function tests were markedly abnormal. Total T_4 was 2.4 $\mu\text{g}/\text{dl}$. The baseline TSH was 329.7 mU/liter, with a grossly exaggerated peak of 1087.32 mU/liter at 30 min. There was some question as to compliance with the prescribed medication. The dosage of L-T₄ was increased to 0.05 mg, and subsequent testing demonstrated normalized thyroid levels. However, her linear growth rate failed to accelerate with thyroid medication alone; therefore, she was enrolled in a research protocol to receive GH treatment.

Transient hyperthyroidism

Subject 101 was enrolled in the study at age 3 yr, 6 months. Her past medical history was significant for surgical closure of an atrial septal defect at age 2 yr. Physical examination revealed stenotic ear canals and down-turned upper and lower lips. Height and weight were 86.5 cm (less than fifth percentile) and 12.5 kg (fifth percentile), respectively. BP was normal (102/40 mm Hg). Goiter and hyperactivity were not observed or reported, and the remainder of the physical exam was unremarkable. Total T_4 was within the normal range at 12.6 $\mu\text{g}/\text{dl}$. T_3 uptake was elevated at 46.2%. However, serial TSH values were suppressed at all time points, ranging from 0.03–0.04 mU/liter. A repeat TSH measurement determined at an independent laboratory 2 months later was also suppressed at less than 0.03 mU/liter, eliminating the possibility of laboratory error. Due to the absence

of other overt manifestations of hyperthyroidism (goiter, hypertension, or irritability), the parents declined treatment, and the child was monitored until her second visit to the study 12 months later. At that follow-up visit, the child still had no symptoms of hyperthyroidism, and the thyroid function tests had normalized. Baseline TSH was 3.17 mU/liter, and the total T₄ was 10.3 μg/dl. Due to her declining growth velocity, the child was enrolled in a clinical trial of GH treatment in children with 18q– and abnormal growth.

Characteristics of the 18q– study cohort

Data for 50 individuals with *de novo* 18q deletions are included in this report, with 25 females and 25 males. The age range of the study cohort ranged from 6 months to 32 yr and included two mother-daughter pairs, both having a deletion of 18q. At the outset, none of the participants had received thyroid or GH treatment.

During the course of the study, six participants were diagnosed with hypothyroidism. All were placed on L-T₄ replacement. One subject was subsequently diagnosed as GH deficient and was prescribed GH treatment. Two of the hypothyroid subjects continued to have poor growth after the initiation of thyroid medication and despite the maintenance of a euthyroid state, but were not classically GH deficient. They were enrolled in an ongoing clinical trial at our center for children with 18q– and declining growth velocities and are currently receiving GH treatment as part of a research protocol.

In one subject, laboratory values were determined that were consistent with hyperthyroidism. However, as discussed above in the case reports, the child had no overt physical symptoms of hyperthyroidism, and all thyroid function tests had normalized by the time of the second visit to our center 12 months later.

Comparison of 18q– TRH testing with TRH testing of normal controls

Table 1 compares TRH testing in the subjects with 18q– with that of the normal control population. Statistically significant *P* values were obtained for the difference between average total T₄ levels in the 18q– and control groups. Highly significant *P* values were obtained for the differences between basal TSH and peak TSH values in the participants with 18q– and controls. However, when the 18q– and control cohorts were subdivided by age and gender, none of the statistical comparisons was statistically significant.

Discussion

To date, this is the largest and most comprehensive study of thyroid function in subjects with 18q deletions. It is also the first to document the relatively common occurrence of thyroid disease in this population. This survey of thyroid dysfunction in individuals with 18q deletions is limited by the cross-sectional design. Although we have longitudinal data for some individuals, we have insufficient numbers of children to permit calculation of incidence rates. The affected children did not exhibit the classical symptoms of hypothyroidism, such as dry skin and hair loss. The absence of the clinical signs of thyroid disease, despite abnormal T₄ and TSH values, has also been documented in Down's and Turner syndromes (9, 11). In addition, the percentage of individuals with 18q– and hypothyroidism reported in this study (12%) may be a significant underestimate of the real prevalence associated with hypothyroidism in 18q–. This is due to the exclusion criteria for this manuscript. Two of the adults who are followed by our center were already diagnosed with hypothyroidism and had been receiving L-T₄ replacement for many years. They were not eligible for this study. Six children developed hypothyroidism, as evidenced

TABLE 1. Comparison of mean T₄ values and mean TSH responses to TRH

	Basal TSH (mU/liter)	Peak TSH (mU/liter)	Peak/basal	Peak time (min)	T ₄ (μg/dl)
18q– vs. controls, total					
18	3.55 ± 0.46	27.86 ± 4.08	8.86 ± 0.61	32.10 ± 1.42	8.72 ± 0.39
C	2.4 ± 0.12	20.29 ± 0.97	9.27 ± 0.43	29.26 ± 1.18	7.84 ± 0.2
<i>P</i>	0.0178 ^a	0.0007 ^a	0.5823	0.3222	0.0455 ^b
18q– vs. controls, males					
18	3.54 ± 0.48	23.55 ± 2.62	7.73 ± 0.56	31.8 ± 2.34	8.78 ± 0.69
C	2.43 ± 0.17	19.26 ± 1.26	8.53 ± 0.55	29.33 ± 1.08	7.58 ± 0.3
<i>P</i>	0.0308 ^b	0.1416	0.3125	0.3371	0.1118
18q– vs. controls, females					
18	3.56 ± 0.81	32.17 ± 7.72	9.98 ± 1.05	32.4 ± 1.66	8.66 ± 0.38
C	2.36 ± 0.18	21.58 ± 1.48	10.19 ± 0.67	29.17 ± 1.04	8.16 ± 0.24
<i>P</i>	0.1471	0.177	0.865	0.0989	0.2627
18q–, males vs. females					
M	3.54 ± 0.48	23.55 ± 2.62	7.73 ± 0.56	31.8 ± 2.34	8.78 ± 0.69
F	3.56 ± 0.81	32.17 ± 7.72	9.98 ± 1.05	32.4 ± 1.66	8.66 ± 0.38
<i>P</i>	0.984	0.2891	0.0561	0.8337	0.8808
18q– vs. controls, 60 ≥ CA < 210 ^c					
18	2.48 ± 0.42	18.83 ± 2.15	9.36 ± 1.28	31.88 ± 1.82	8.81 ± 0.39
C	2.65 ± 0.39	20.00 ± 1.51	8.23 ± 0.57	29.50 ± 1.13	8.42 ± 0.28
<i>P</i>	0.7672	0.66	0.4179	0.267	0.4122

Values are the mean ± SE. C, Controls; M, males; F, females.

^a 0.01 level of significance.

^b 0.05 level of significance.

^c These data compare the subset of children with 18q– who fall within the same chronological age (CA; in months) range as the control group of children.

by elevations of TSH, after initiation of GH treatment. Due to these exclusions, hypothyroidism may be more common in subjects with 18q– than was found in this study cohort.

We do not know the mechanism leading to thyroid dysfunction in these children; however, it appears from the absence of blunted or delayed peak times in our cohort that the primary dysfunction is thyroidal, rather than pituitary or hypothalamic central hypothyroidism (17).

In this population, the finding of both hypothyroidism and hyperthyroidism suggests autoimmune disease as a possible mechanism for the thyroid dysfunction in these individuals. Antibodies have not been routinely determined in our studies. However, hyperthyroidism with elevated autoantibodies has been previously associated with 18q– in a case report (18).

Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is the most common type of acquired hypothyroidism in children, with an estimated prevalence in the pediatric population of one in 500 to one in 1000 (19). Repeated episodes of thyroiditis over several years could result in the hypothyroidism seen in the majority of the adults in our study with 18q deletions. Additional support for this hypothesis is that other autoimmune disorders have been genetically linked to chromosomal region 18q21, including type I diabetes, rheumatoid arthritis, and Graves' disease (20–22).

Longitudinal case studies demonstrate that thyroid status in these patients is not static and may change from a euthyroid to a hypothyroid state over time. Routine testing and maintenance of the euthyroid state are particularly important in those who are not growing well and/or who are at risk for developmental delays. Our findings clearly indicate the need for annual thyroid function screening of all individuals with 18q deletions. Free T₄ and baseline TSH measurements should be adequate, because all the identified cases of hypothyroidism have been primary. More complicated approaches to the diagnosis of thyroid dysfunction in this population, such as TRH or nocturnal surge testing, appear to be unnecessary. Research is in progress to identify possible candidate genes and the mechanisms that may be responsible for this phenotype.

One of the goals of our research was to define the key genes responsible for the phenotype in individuals with 18q–. The first step in this process is to identify a critical region of the chromosome that is hemizygous (present in one copy) in all of the subjects with the phenotype of interest. In this study, 45 of 50 participants were completely genotyped at the time of this analysis (data not shown). This genotyping was performed using a combination of PCR-based polymorphic marker analysis and quantitative real-time PCR. All four individuals with hypothyroidism were genotyped, and all had terminal deletions. Therefore, the participant with the smallest terminal deletion defined the hypothyroidism critical region, which was 13.3 Mb, extending from their breakpoint to the end of the q arm. Thirty-nine of the 45 individuals genotyped were hemizygous for this hypothyroidism critical region. Because only four of the 39 individuals hemizygous for this critical region had hypothyroidism, this phenotype was 10% penetrant. This low penetrance is in contrast to the brain dysmyelination phenotype, in which 100% of the par-

ticipants with 18q deletions who are hemizygous for that critical region have dysmyelination (23).

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Address all correspondence and requests for reprints to: Dr. Daniel E. Hale, Division of Endocrinology and Diabetes, Department of Pediatrics, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78229. E-mail: hale@uthscsa.edu.

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