

Editor's comment: This is a very large and carefully performed epidemiologic study. The finding that women with TS have a relative risk profile similar to that of postmenopausal women suggests ways in which pediatric and adult endocrinologists might intervene to significantly alter this morbidity. In Denmark, it is suggested that most women with TS receive lifelong sex steroid replacement

therapy. The specific age at which therapy is initiated remains somewhat controversial as pediatric endocrinologists attempt to maximize the height of these young girls. It is important, however, to stress to these young girls the importance of continuing therapy throughout adulthood as a possible protection against excess morbidity.

William L. Clarke, MD

Relative Risk of Endocrine Diseases in Turner Syndrome

Diagnoses (ICD-8)	Observed	Expected	RR (95% CI)
Endocrine diseases, overall (240-258)	51	10.47	4.87 (3.63-6.41)
Thyroid diseases, overall (240-246)	10	4.98	2.00 (0.96-3.69)
Thyrotoxicosis (242)	3	1.50	2.01 (0.41-5.86)
Hypothyrosis (244)	3	0.52	5.80 (1.20-16.94)
Thyroiditis (245)	3	0.81	16.60 (3.42-48.50)
Insulin-dependent diabetes mellitus (249)	9	0.78	11.56 (5.29-21.95)
Noninsulin-dependent diabetes mellitus (250)	13	2.88	4.38 (2.40-7.72)
Miscellaneous endocrine diseases [251-258 (-251.13-15)]	15	1.72	8.71 (4.87-14.36)
Parathyroid disease (252)	1	0.14	7.25 (0.18-40.37)
Hypoglycemia (251.00)*	2	0.57	3.51 (0.43-12.69)

* Based on diagnosis on the 5-digit level.

CI, confidence interval

RR, relative risk

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Growth Failure in Prader-Willi Syndrome Is Secondary to Growth Hormone Deficiency

Thacker and colleagues conducted a retrospective study of 16 children who met the diagnostic criteria for Prader-Willi syndrome (PWS). All had hypotonia during the neonatal and infantile periods, failure to thrive, rapid weight gain after the first year of life, dwarfism, hypogonadism, developmental delay, and hyperphagia. The 15q11-13 chromosomal abnormality had been identified in 13 of the 16. Growth hormone deficiency (GHD) as defined by growth hormone (GH) response <10 ng/mL on a provocative test was present in 12 of the 16. All the nonobese patients were GHD. Seven of the children were treated with recombinant human GH (rhGH) at a dose of 0.3 mg/kg/wk, and rhGH therapy continued for 6 to 23 months (see Table). All 7 children treated with rhGH had significant increases in their growth velocity. The authors state that although their study was retrospective, it suggests that the secretion of GH in PWS children is related to abnormalities of the hypothalamic-pituitary axis rather than to their obesity per se. This is based in part on the association of low insulin-like growth factor 1 (IGF-1) levels in most, which is not attributable to obesity, plus low GH responses to pharmacologic stimulation.

Thacker M, et al. *Hormone Res* 1998;49:216-220.

Annualized 6-Month Pretreatment and Posttreatment Growth Velocities (GV) in Prader-Willi Syndrome Children Treated With Recombinant Human Growth Hormone at a Dose of 0.3 mg/kg/wk

Patient No.	Pretreatment GV (cm/y)	Posttreatment GV (cm/y)
5	4.5	10.00
9	5.16	13.92
10	3.90	13.20
11	3.60	12.00
14	0.00	6.76
15	1.80	12.30
16	2.50	7.66

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Editor's comment: This interesting report describes another clinical syndrome, PWS, in which GHD plays a major role. The children in the study were well characterized both by clinical and laboratory criteria. These investigators have made a worthy retrospective analysis of a potential etiology of GHD and rhGH

treatment in PWS. The lack of a response to provocative stimuli and subsequent increases during rhGH therapy underscore the importance of evaluating these children when seen in the clinical situation.

William L. Clarke, MD

Growth Hormone Treatment of Children With Prader-Willi Syndrome Affects Linear Growth and Body Composition Favorably

Lindgren et al studied 29 prepubertal children with Prader-Willi syndrome (PWS), all of whom had a paternal deletion or a maternal disomy of chromosomal region 15q11-13, hypotonia, hypogonadism, hyperphagia, obesity, short stature, psychomotor retardation, behavioral abnormalities, and dysmorphic features. In addition, 10 control healthy obese prepubertal children were studied. Growth hormone (GH) was sampled every 30 minutes for 24 hours and plasma insulin-like growth factor 1 (IGF-1), glycosylated hemoglobin, and fasting insulin and glucose were determined. Body mass and body mass index were calculated. Fat-free mass was determined by bioelectrical impedance and by dual energy X-ray absorptiometry. Fifteen of the 29 children with PWS were treated with GH at a dose of 0.1 IU/kg/d (0.23 mg/kg/wk) SC for 1 year. The others served as a second control group.

The obese control children were tall and had normal increased serum IGF-1 levels, whereas the PWS children were short with normal or low IGF-1 levels. However, 24-hour GH secretion was low in both PWS and obese control children. During the 1 year of treatment, significant increases in height velocity were observed. Serum IGF-1 levels increased as well. Body mass index decreased and a 25% reduction in fat mass and a 30% increase

in fat-free mass were observed. Fasting insulin levels increased significantly in the treated group, but fasting glucose and glycosylated hemoglobin levels were unchanged throughout the study. The authors state that these studies demonstrate that the majority of these patients were GH deficient and that GH deficiency is part of the hypothalamic dysfunction observed in this disorder.

Lindgren A, et al. *Acta Paediatr* 1998;87:28-31.

Editor's comment: This description of the beneficial effects of GH in children with PWS supports those of Thacker et al recorded in the previous abstract. The children in the current study did not undergo stimulation tests, and thus their findings are not entirely biochemically comparable to those of Thacker et al. However, the growth responses of both groups were similar, and the additional finding of increased fat-free mass and decreased fat mass in the current study (Lindgren) demonstrates an additional important benefit of GH in these children.

William L. Clarke, MD

Thacker M, et al. *Hormone Res* 1998;49:216-220.

Fathers and *FGFR3* Mutations

Achondroplasia is the prototype of short-limb dwarfism and is by far the most common form of dwarfism in humans. It results from activating mutations of the gene encoding fibroblast growth factor receptor 3 (*FGFR3*). The vast majority of cases result from new mutations, which in all cases involve nucleotide 1138 in exon 10 of this gene. This nucleotide is thus one of the most mutable nucleotides in the entire human genome.

The association of sporadic cases of achondroplasia with advanced paternal age has been recognized for years, suggesting that mutations at this site preferentially occur during spermatogenesis. The Wilkin group has now demonstrated this to be true.

Wilkin et al studied 97 families in which a child with achondroplasia had been born to parents of normal stature. They first identified a DNA polymorphism near the mutation site in the *FGFR3* gene. This enabled them to potentially determine if a mutation in a given case had occurred on the maternal or paternal *FGFR3* allele. The analysis was informative in 40 of the 97 families, revealing that the mutation occurred on the paternal allele in all 40 cases. In other words, the mutation had virtually always occurred in the *FGFR3* gene inherited from the father.

The authors discuss differences between spermatogenesis and oogenesis, noting that meiotic errors can accumulate to a much greater extent in the former because male germ cells divide much more often than do female germ cells. However, they acknowledge that the reasons why mutation of this particular nucleotide is so much more common during spermatogenesis are unknown.

Wilkin DJ, et al. *Am J Hum Genet*. 1998;63:711-716.

In Future Issues

Surfing the Web for Information on Genetic and Hormone Disorders

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