

Basically 2 groups of patients were studied: (1) 39 patients with unequivocal RSS and, (2) 166 patients with unexplained growth retardation but who did not have RSS. The latter group was divided into 2 subgroups: (2a) those with IUGR and postnatal growth retardation (PNGR) and, (2b) those with only PNGR. For final analysis, the RSS patients were separated into 2 subgroups also: (1a) RSS with matUPD7, and (1b) those without mat-7-UPD.

Only 6 of the 205 patients studied had matUPD7 and all had RSS. Thirty-three of the 39 in the RSS group did not have UPD. Comparison of these two groups revealed that RSS infants (with or without matUPD7) were significantly shorter at birth than infants in group 2a and 2b. The birth weights and lengths of RSS patients with or without matUPD7 were equally small. However, birth weights did not differ between groups 1a, 1b, and 2a. Notable difference of parental age at birth was observed between group 1a and the other 3 groups. MatUPD7 patients had significantly higher ($p < .05$) maternal age (38 years) and paternal age (40 years) than those in the other 3 groups.

Midparental heights were near average for all groups. Maternal obstetrical complications known to possibly restrict fetal growth (e.g. toxemia, high blood pressure, and alcohol or tobacco use) were reported in 5 (15%) of 33 of group 1b, 24 (26%) of 91 in group 2a, and only in 5 (7%) of the 75 mothers of the PNGR (group 2b).

The authors point out that matUPD7 and growth hormone deficiency (GHD) can occur together as can

GHD and other causes of IUGR and PNGR, and emphasize that other metabolic disorders do not exclude matUPD7. MatUPD7 has been reported in 3 patients with cystic fibrosis, all of which were exceedingly short. Consequently the authors advise screening for matUPD7 if abnormally short stature occurs conjointly with cystic fibrosis or other recessive disorders mapped to chromosome 7. However, because matUPD7 is rare among IUGR and PNGR patients, except in RSS, screening will be primarily helpful in this group of RSS patients.

Hannula K, et al. *Pediatrics* 2002;109:441-448.

Editor's Comment: *The long-term natural history of matUPD7 is not yet clear. Fertility and possible transmission of UPD has not been evaluated. For these reasons, and others such as responsiveness to various therapies, screening in appropriate instances is important. All RSS patients should be screened and those RSS patients with and without matUPD7 should be further evaluated to determine the molecular biological differences between the two groups. The authors discuss some possibilities in their manuscript. The entire manuscript is very enlightening and is recommended both for theoretical considerations and factual data.*

Judith G. Hall, OC, MD

Quality of Life and Self-Esteem in Children Treated for Idiopathic Short Stature

This study from Leiden University in the Netherlands dealt with changes in health-related quality of life (HRQOL) and self-esteem in children with idiopathic short stature (ISS) participating in a study on the effects of growth hormone (GH) treatment. There were 36 pre-pubertal children who were randomly assigned to a treatment or to a control group. Children, their parents and their pediatricians completed a HRQOL and a self-esteem questionnaire, 3 times in 2 years. The data indicated that children with ISS did not have lower scores at the start as compared with the normal population, except for social functioning. The pediatricians noticed an improvement in HRQOL in the children in the treatment group. Those in the treatment group did grow significantly more than those in the control group. However, the parents and the children being treated reported no change in HRQOL. Indeed, in some instances they reported being worse than before. The child's satisfaction with height was more related to HRQOL than was measured height. The authors

concluded that the assumption that growth hormone treatment improves HRQOL or self-esteem in children with short stature could not be supported by this study.

Theunissen NCM, et al. *J Pediatr* 2002;140:507-515.

First Editor's Comments: *It is widely assumed that short stature may be a handicap and that this condition may result in psychosocial problems, such as ridicule, and mascotism. Indeed, short people might be victims of discrimination and prejudice, often referred to as "heightism". For that reason, many have opted to receive GH with the intent to accelerate growth and improve the final adult height, and in that way improve their psychosocial status. The response to GH treatment in these children appears to be modest, resulting in a possible gain in final height of 5–9 cm, after many years of treatment. However, few studies have approached the concept of HRQOL as an outcome measure of this treatment. In this study, children with a height of more*

than two standard deviations below the mean for age and sex, who were not GH deficient, were found to have appropriate HRQOL and self-esteem, and did not show improvements after GH treatment. The parent's opinion about their social competence after treatment was also not changed. Of interest was the lack of agreement between the informants, who were the patients and parents, with the pediatrician's perception of the effects on quality of life after GH. The relationship between stature, growth, HRQOL and self-esteem might be determined by the expectations of the participants rather than by the improvements in growth. These children, as well as their parents, might have had unrealistic expectations and, therefore, not be satisfied with the treatment, despite improved standard deviation scores for height. Therefore, when we undertake treatment of a non-growth hormone deficient short child, we should consider aspects other than height. GH treatment should not be initiated just because the child is short. An interesting editorial accompanied this article and was written by Basil J. Zitelli in the same issue of the journal, and the reader is encouraged to review that as well. (*Journal of Pediatrics* 2002;140:493-495).

Fima Lifshitz, MD

Second Editor's Comment: Dr. Zitelli in his commentary points out with emphasis that offering

children and parents therapy for short stature raises expectations of success. Motivation to be included in GH trials frequently involved the hope of gaining height, yet if expectations were not met through therapy, poor self-esteem and parental anxiety and disappointment were acutely felt by the child. With the variability and unpredictability of results for any particular child, GH therapy becomes an intervention that may be more detrimental than the original complaint of short stature.

Investigators have added another layer of therapy to enhance growth. To delay epiphyseal fusion, gonadotropin releasing hormone agonists have been added to GH treatment regimens. This may potentially compound the iatrogenically introduced fear in the normal short child of being abnormal or affected with a disease that requires 2 medications to treat.

The last issue (GGH 2002 Vol 18:3) has an abstract and commentary regarding the use of LHRHa in advanced puberty. The conclusion of the authors was "these data suggest that advanced puberty (as differentiated from sexual precocity defined as sexual development in girls before the age of 8 years and boys below 9 years) decreases the growth potential by about 5 cm and that GnRHa therapy does not prevent this".

Robert M. Blizzard, MD

A Gene as a Major Cause of Sotos Syndrome has been Identified

Sotos syndrome is a relatively common neurologic disorder characterized by prenatal and postnatal overgrowth, advanced bone maturation, large skull with acromegalic features, and significant developmental delay. Most cases are sporadic, but autosomal dominant inheritance has been suggested in some instances and autosomal inheritance in a few rare instances. Reports of balanced translocations have pointed to several chromosomal sites as the location of a gene responsible for the syndrome. One of these has led to the identification of mutations of a nuclear hormone receptor cofactor as a major cause of this syndrome.

Kurotaki et al analyzed DNA from a patient with a de novo translocation 46,XX,t(5;8)(q35;q24.1) that had been reported previously by Imaizumi et al. From analysis of a series of overlapping clones, a contig, that covered the break point, they identified a partial sequence that corresponded to a gene originally cloned in mice, *NSD1*. They then isolated and characterized the human *NSD1* showing that it encoded a protein of 2,696 amino acids that is expressed in many tissues including fetal brain, skeletal muscle and kidney, and that the 5q35 breakpoint is located within *NSD1*.

The group next analyzed DNA from 38 patients with the clinical diagnosis of Sotos syndrome. De novo point mutations that would predict truncated gene products with loss of function were identified in four individuals. Fluorescent in situ hybridization (FISH) analysis revealed a common 2.2 Mb deletion in 18 and a smaller deletion in one of 30 patients in whom a suitable chromosomal spread was available. These deletions included the entire *NSD1* gene. In total, a loss of function mutation or a deletion of *NSD1* was found in 77% of patients implicating haploinsufficiency of *NSD1* as a cause of Sotos syndrome.

NSD1 is thought to act as a co-activator or co-repressor of nuclear hormone receptors, such as the androgen receptor, depending on the promoter context of the target gene and the cellular context. In other words, in one cell type *NSD1* may interact with a combination of regulatory factors unique to the cell type to activate a target gene, whereas it may interact with another set of factors to inhibit expression of target genes in another cell type. The mutations thus alter expression of target genes in relevant tissues.

Clinically, the authors state that the identification of a deletion or mutation of this mutated gene on