

## Leprechaunism and the Insulin Receptor Gene

Leprechaunism was first described in 1948 by Donohue<sup>1</sup> as a rare autosomal recessive inborn error of metabolism characterized by severe intrauterine and postnatal growth retardation, elfin facies, decreased subcutaneous and muscular tissue, hirsutism, and prominent genitalia.

Patients with leprechaunism have hyperinsulinism due to severe insulin resistance. The insulin resistance in this syndrome has been associated with an inherited defect in a high-affinity insulin receptor.<sup>2</sup> The central role of insulin is to regulate carbohydrate, lipid, and protein metabolism as well as promote cell growth. Insulin is known to stimulate embryonic reproductive tissue and insulin receptors are expressed very early in embryonic development.

Molecular studies in children with leprechaunism had shown homozygous nonsense or compound heterozygous mutations in the insulin receptor gene,<sup>3</sup> but homozygous deletions had never been reported. In all previously described cases, there was some residual function of the insulin receptor, and it was generally believed that complete loss of insulin receptors was incompatible with fetal life.

Recently, Krook et al<sup>4</sup> and Wertheimer et al<sup>5</sup> reported DNA

studies on the only patients known thus far to have a homozygous, complete deficiency mutation in the insulin receptor gene. Both patients presented with normal organogenesis, survived beyond term, and had the typical features of leprechaunism.

The authors suggested that although the insulin receptor is important for intrauterine growth, neurologic development and organogenesis can occur in the absence of functional insulin receptors.

1. Donohue WL. *J Pediatr* 1948;32:739.
2. Elsas LJ, et al. *Am J Hum Genet* 1985;37:73-88.
3. Taylor SI, et al. *Endocr Rev* 1992;13:566-595.
4. Krook A, et al. *Lancet* 1993;342:277-278.
5. Wertheimer E, et al. *Nature Genetics* 1993;5:71-73.

**Editor's comment:** *There may be many complex interactions and buffering mechanisms at work during early embryonic development allowing an embryo with a severe genetic deficiency such as this to survive. Some other as yet unknown pathway must compensate for the absence of insulin receptors.*

Judith G. Hall, MD

## Mild to Moderate Zinc Deficiency in Short Children: Effect of Zinc Supplementation on Linear Growth Velocity

In zinc-deficient subjects total body clearance of zinc is increased. Two hundred twenty children with short stature underwent evaluation to rule out evidence of systemic or endocrinologic disorder and to measure zinc clearance kinetics (height for age < -2 SD). Twenty-one prepubertal children had normal serum zinc concentrations but an increased body zinc clearance rate of  $\geq 20$  mL/kg/h (normal subjects =  $15.1 \pm 0.6$  mL/kg/h). These children were randomly divided into 2 groups, one of which received zinc sulfate 5 mg/kg/d orally for 6 months, the other serving as a control group. After 6 months of therapy, the zinc-treated subjects had significantly increased growth rates (treated: from -3.14 to 2.26 SDS vs controls: from -2.29 to -2.42 SDS) and increased circulating IGF-1 and osteocalcin concentrations in comparison to the control subjects. No cause for zinc deficiency (eg, diabetes mellitus, sickle cell disease, chronic inflammatory bowel disease) was apparent in these 21 children, nor did they have decreased dietary intake of zinc. The authors suggest that measurement of body zinc kinetics may reveal children with mild zinc deficiency. They recommend a trial of zinc therapy in short children with no identifiable abnormality, even if the serum concentration of zinc is normal.

Nakamura T, et al. *J Pediatr* 1993;123:65-69.

**Editor's comment:** *Zinc deficiency leads to hyposmia and hypogeusia and thus to decreased caloric intake. It has been most apparent in children and adolescents in Middle and Far Eastern countries where zinc intake is low and intestinal absorption is inhibited by zinc binding agents.<sup>1</sup> The present report suggests that mild zinc deficiency occurs in 10 percent of short*

*Japanese children. Zinc deficiency in North America has been reported in low income infants and children,<sup>2</sup> but its frequency in otherwise normal short children may not be high.<sup>3</sup> Confirmation of these observations in North American children is necessary before zinc therapy can be recommended routinely.*

Allen W. Root, MD

1. Sandstead HH. *Am J Dis Child* 1991;145:853-859.
2. Walravens PA, et al. *Am J Clin Nutr* 1983;38:195-201.
3. Solomons NW, et al. *Pediatr Res* 1976;10:923-927.

**2nd Editor's comment:** *Zinc deficiency as a possible cause of growth retardation and/or delay in adolescent sexual development first was considered seriously by Prasad working in Iran and, later, Egypt in the 1960s. Subsequently others have considered, and promoted in some instances, zinc deficiency as an etiologic factor in some children with unexplained short stature. I have remained a skeptic because the data have been unconvincing. This study is a credible attempt to clarify the role of zinc in relation to growth. As Dr. Root states, further studies are important and necessary before zinc supplements are used in the U.S. as therapy for growth failure. Six month studies, even when well controlled, are inadequate to derive conclusions that a particular agent is effective in promoting growth. Within the next year, the Editorial Board will invite 2 experts to write point/counterpoint articles regarding zinc deficiency.*

Robert M. Blizzard, MD