

Effects of Therapy in X-Linked Hypophosphatemic Rickets

Verge et al prospectively studied 24 children (ages 1 to 16 years) with X-linked hypophosphatemic rickets who were treated from 0.3 to 11.8 years with daily calcitriol (25.6 ± 16.9 ng/kg/d) and oral phosphate (100 ± 34 mg/kg/d) administered in divided doses every 4 hours. Patients were evaluated every 3 months for serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, and alkaline phosphatase and for height. Calcium, phosphorus, and creatinine were measured in 24-hour urine samples and in random urine samples collected to determine calcium to creatinine ratios. Glomerular filtration rates were measured in 20 patients. Annual height measurements were converted into height standard deviation scores (SDSs) according to data from the US National Center for Health Statistics. To exclude the effects of variation of the onset of puberty and the difficulty of measuring small infants, the first measurements reported were after the age of 2 years and the last were taken before the age of 10 years in girls and 12 years in boys. The mean interval of study of these 13 patients was 5.0 ± 2.3 years.

Growth data were compared to those of 16 untreated prepubertal Australian patients with X-linked hypophosphatemia whose height SDSs were previously reported. Height SDSs also were computed according to the standards of Tanner. Renal ultrasonography was performed every 6 to 12 months. Duration of therapy, age at which therapy was begun, mean and total doses of vitamin D and phosphate, mean serum calcium, number of episodes of hypercalcemia, mean and maximum levels of urinary calcium and phosphorus excretion, number of episodes of hypercalciuria and the mean and maximal products of urinary calcium and phosphorus concentrations were examined as potential risk factors for nephrocalcinosis.

Patients treated with combined calcitriol and oral phosphate for at least 2 years had a mean height SDS (method of Tanner) of -1.08 as compared with -2.05 for the untreated control group ($P=0.01$). However, the mean change in height SDS of the 13 patients treated for at least 2 years changed only from -1.42 to -1.25 ($P=0.05$). When the change in the height SDSs were analyzed only with regard to the period of calcitriol and phosphate therapy, mean height SDSs increased from -1.58 to -1.25 ($P=0.05$). No significant correlation was found between the change in the height SDSs and the duration of treatment or the age at which it began. Nineteen of 24 patients (79%) demonstrated nephrocalcinosis on renal ultrasonography. Regression analysis demonstrated a significant association between nephrocalcinosis and mean daily phosphate dose ($r=0.60$, $P=0.002$). Mean serum calcium concentrations in the 24 patients ranged between 2.15 to 2.53 mMol/L (8.6 to 10.1 mg/dL). Fifteen patients had serum calcium concentrations of more than 2.5 mMol/L (10.0 mg/dL) on 1 or more occasions. Eight of the 19 for whom urinary measurements were available had 1 or more episodes of hypercalciuria. These received significantly more calcitriol than those who never had hypercalciuria (29.9 vs 17.3 ng/kg/d, $P=0.007$); 4 of 20 had a decrease in glomerular filtration rate.

The authors conclude that since X-linked hypophosphatemic rickets is a benign disease compatible with a normal life span, the potentially serious side effect of nephrocalcinosis requires that the treatment regimen be reevaluated. Since the advent of combination therapy with calcitriol and phosphate, few patients now require surgical osteotomy; however, their data demonstrate only a modest effect on final height. They further suggest that since the growth pattern of untreated patients has not been well

documented, a prospective controlled trial of combination therapy needs to be undertaken to evaluate its effect on linear growth. The authors recommend the conservative use of phosphate and calcitriol during therapy and regular monitoring for both nephrocalcinosis and periodic determination of glomerular filtration rates.

Verge CF, et al. *N Engl J Med* 1991;325:1843.

Editor's comment: *This very important and interesting article contributes significantly to the information concerning the effects of calcitriol and phosphate in X-linked hypophosphatemic rickets. The authors are correctly concerned with the high frequency of nephrocalcinosis in their patients.*

An accompanying editorial (N Engl J Med 1991;325:1875) by Glorieux reviews the classification and therapy of all forms of rickets. Glorieux notes that data developed by Verge et al confirm earlier reports suggesting that phosphate and calcitriol improve the growth rate of children with X-linked hypophosphatemic rickets. However, at least one retrospective study (Stickler GB et al. Lancet 1989;2:902) concluded that failure of treatment to promote growth and the risks of renal failure suggested that it might be better not to treat these patients at all. Glorieux does not agree with Verge et al that a randomized, placebo-controlled trial should be undertaken. He points to the central role of hypophosphatemia in retarding growth as demonstrated by Harrison et al in 1966 (Am J Dis Child 1966;112:290-297). In that report, a girl with dwarfism and X-linked hypophosphatemic rickets had severe vitamin D intoxication that permanently reduced her glomerular filtration rate; her serum phosphate had increased to a normal level. Surprisingly, her final adult height reached the 50th percentile. Glorieux concludes that the frequent assessment of renal function is important in caring for these individuals.

Rickets and growth was recently reviewed in GGH (7;4:1-3). In that review it was suggested that if treatment starts before the age of 5 years, catch-up growth can be achieved. Readers need to realize that not all investigators agree on the extent of treatment benefit, but all agree that close observation is needed.

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GROWTH, Genetics, & Hormones is published under an educational grant from Genentech, Inc.