

Endocrinological and Auxological Abnormalities in Children with Optic Nerve Hypoplasia: A Prospective Study

Ahmad and associates performed a prospective observational study of 47 children with optic nerve hypoplasia (ONH [deMorsier's syndrome]) who presented to the Pediatric Ophthalmology clinic at Children's Hospital Los Angeles. Subjects 3 years of age and under were enrolled in the study and were followed annually until 5 years of age for visual growth and neurodevelopment outcomes. Although 170 subjects have been enrolled, the data presented are for the first 47 subjects to have completed the study. All subjects had baseline endocrinological, electrophysiological, and neuroradiological findings. Growth hormone (GH) status was defined by insulin-like growth factor (IGF)-I and/or IGF binding protein (BP)-3 or subnormal GH responses to glucagon stimulation. Height (or length) and weight were measured at each visit.

Hormonal dysfunction was found in 71.7% of these children. A growth hormone axis abnormality was observed in 64.1%, hyperprolactinemia in 48.5%, hypothyroidism in 34.9%, adrenal insufficiency in 17.1%, and diabetes insipidus in 4.3%. There was no association between endocrine abnormalities and unilateral versus bilateral ONH. In addition, the absence of the septum pellucidum or other pituitary abnormalities was not associated with endocrinologic function. There was no statistically significant difference in the median start versus end height SDS, but there was a significant increase noted for the median weight SDS. In the cohort, 44.4% were >85th percentile for weight at the end of the study. There were 27 subjects who had both IGF-I and IGFBP-3 assessed. The data were dichotomized as "both normal" or "at least one abnormal hormone surrogate." Using this division, there was no significant difference in the median change in height, weight, or in body mass index (BMI) over time. Eight of the subjects received GH replacement. Of the 19 subjects not receiving GH therapy, 10 had one abnormal GH surrogate. Although

the change in height was statistically significant for those receiving GH therapy, those children who did not receive GH treatment continued to grow, with significant BMI increase.

The authors pointed out that there is an unclear understanding of the etiology of ONH. The current study which confirmed a high prevalence of endocrinopathy showed no association between endocrine abnormalities and unilateral versus bilateral ONH, although subjects with a pituitary abnormality on neuroimaging had an endocrinopathy. Seventy-one percent of those with a normal pituitary gland also had an endocrinopathy. The authors speculated that one of the possibilities for explaining the weight gain might be a decreased lipolytic activity resulting from the absence of GH, as suggested in patients with Prader-Willi syndrome.

Ahmad T, Garcia-Filion P, Borchert M, Kaufman F, Burkett L, Geffner M. Endocrinological and auxological abnormalities in young children with optic nerve hypoplasia: a prospective study. *J Pediatr*. 2006;148:78–84.

Editor's Comment: *This is a very interesting observational study, which provides important information for pediatric endocrinologists, geneticists, and pediatricians who care for children with ONH. Importantly, it demonstrates that it is not sufficient to evaluate these children endocrinologically at only one point in time. In addition, it is not sufficient to assume that these children do not have GH deficiency because they continue to experience linear growth. Indeed, the authors have shown that many of these children continue to grow linearly and to gain excessive weight. The suggestion that these children may be candidates for GH treatment regardless of their GH surrogate status is appealing and deserves further investigation.*

William L. Clarke, MD

Growth Hormone Receptor Exon-3 and Response to Growth Hormone Treatment

A polymorphism in the growth hormone receptor (GHR) gene, the presence or absence of exon-3, has recently been shown to influence the 1- and 2-year growth response to recombinant human growth hormone (rhGH) therapy in children without GH deficiency (GHD). To study the influence of GHR-exon-3 genotype on the short- and long-term response to rhGH therapy in children with GHD, Jorge et al genotyped and followed the first year growth velocity following rhGH treatment in 58 children (36 boys, 22 girls) who remained prepubertal and the adult height of 44 patients (included 27 patients analyzed for the first-year response) after 7.5 ± 3.0 years of treatment.

Clinical and laboratory data at the start of treatment

were indistinguishable among patients carrying *GHR*-exon-3 genotypes. Patients carrying at least one exon-3 deleted *GHR* (*GHRd3*) allele had a significantly better growth velocity in the first year of treatment (12.3 ± 2.6 vs 10.6 ± 2.3 cm/year, $p < 0.05$) and achieved a taller adult height (final height SDS of -0.8 ± 1.1 vs -1.7 ± 1.2 , $p < 0.05$) when compared with patients homozygous for *GHR* full-length alleles (*GHRfl*). They conclude that patients with GHD who are homozygous for *GHR* exon 3fl were less responsive to short- and long-term rhGH therapy. Approximately half of the population is homozygous for *GHRfl*; thus, future studies adjusting rhGH therapy to genotype may improve outcome to therapy.