



Nedd4^{-/-} mice die immediately after birth, and *Nedd4*^{+/-} and *Nedd4*^{+/-} mice exhibit intrauterine growth retardation. No mice homozygous for disruption of the *Nedd4* gene were found 2 or 3 weeks after birth. Ratios of heterozygotes and homozygous mutants were thus assessed at earlier time points: (A) 12.5 dpc, (B and C) 18.5 dpc, and (D) immediately after birth. Both heterozygotes and homozygous mutants showed signs of intrauterine growth retardation as early as 12.5 dpc (A) and at late gestation [18.5 dpc (B) and (C)]. At the time of birth [postnatal day 1 (D)], the body weights among three genotypes differed significantly: *Nedd4*^{-/-} body weight averaged 64 to 68% lower relative to that of wild-type littermates; heterozygote body weight averaged about 15 to 20% reduction in body weight relative to that of wild-type littermates. In (C) and (D), the numbers of animals used for the analyses are shown in parentheses; the body weight was significantly different between groups of mice, with P values indicated. Reprinted with permission Cao XR, et al. *Sci Signal*. 2008;1: ra5. Copyright © AAAS 2008. All rights reserved.

to insensitivity to IGF-I and an intact IGF1R is encountered. A polymorphic variant or mutation in either one of these proteins might also account for impaired intrauterine

growth in some small-for-gestational age neonates.

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Growth Hormone Deficiency: Transient or Permanent?

In this multicenter study, Berberoglu and colleagues tried to assess the need for continuation of growth hormone (GH) treatment in adulthood after growth is completed and also to evaluate factors that would predict persistent GH deficiency (GHD). A total of 70 (31 female, 39 male) GHD patients were included in the study; 52 patients (74%) had isolated GHD and 18 patients (26%) had multiple pituitary hormone deficiency (MPHD). The initial diagnosis was based on a peak GH level <10 ng/mL in 2 pharmacological tests. GH treatment was discontinued in these patients when growth velocity during the

previous year decreased to less than 2 cm and the bone age had reached greater than 14 years in girls, and greater than 16 years in boys, and after completion of puberty. All patients were re-tested by insulin tolerance test (ITT) at least 6 weeks after discontinuation of the replacement treatment. Serum insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 concentrations were determined at the same time. If GH peak during ITT was <3 ng/mL, the patient was diagnosed to have severe permanent GHD.

Among the patients with isolated GHD, 9 patients

(17.3%) were found to have persistent GHD and 43 (82.7%) to be transiently GH deficient. On the other hand, among patients with MPHD only 2 patients (11.1%) were transiently GH deficient.

None of the parameters differed significantly with respect to gender. There were significant positive correlations between peak GH and IGF-I, and IGFBP-3 levels in all patients (IGF-1 $r=0.297$, $p=0.036$; IGFBP-3 $r=0.45$, $p=0.03$). The IGF-I and IGFBP-3 SDS values were lower in the group that had peak GH values <3 ng/mL. When the cut-off was taken as -2 SD, specificity and sensitivity of IGF-I in confirming persistency of GHD were 65.7% and 73.3%, respectively. Its positive predictive value and negative predictive value were 33.3% and 85.2%, respectively. For IGFBP-3, specificity and sensitivity were 84%, and 60%, respectively. The positive and negative predictive values were 60%, and 84%, in the same order. Finally, while the negative predictive values were high for both of these parameters, an IGFBP-3 value below -2 SD was found to be more specific than an IGF-I value below -2 SD.

The data in this study confirmed that there were no auxological and clinical signs to predict the transiency or the persistence of GHD except for a history of organic disease and presence of MPHD. The authors concluded that most patients with childhood onset GHD were idiopathic and GHD was frequently transient in this group of patients. In contrast, GHD was persistent in patients with MPHD. They emphasized the high negative predictive values for IGF-I and IGFBP-3 (85.1% and 84%, respectively) suggesting that normal IGF-I and IGFBP-3 levels highly exclude the diagnosis of GHD.

Berberoglu M, Siklar Z, Darendeliler F, et al. Evaluation of permanent growth hormone deficiency (GHD) in young adults with childhood onset GHD: a multicenter study. *J Clin Res Ped Endo*. 2008;1:30–37.

Editor's Comment: *The question of how to confirm the diagnosis of adult GHD in an adolescent patient who has completed linear growth is still being debated. The Growth Hormone Research Society guidelines suggest a peak GH response on ITT of <3 ng/mL as being diagnostic*

of GHD in adulthood.¹ Although patients with MPHD have peak GH levels <3 ng/mL, it is not clear whether this value can confirm adult GHD exactly. In addition, despite the high negative predictive values of IGF-I and IGFBP-3, the use of serum IGF-I and IGFBP-3 alone to predict GHD cannot be recommended. The majority of children with GHD, when retested as adults, do not have the classical severe GHD.² This high incidence (70%) of normal GH responses on retesting has been shown in patients with idiopathic and isolated GHD.³ This finding indicates that the organic etiologies are often severe and can be assumed to be permanent at the beginning of the therapy. Therefore, those patients with organic MPHD could be excluded from retesting.

The patients who have peak GH cut-off values between 3-5 ng/mL might be GH deficient as well. In fact, in the transition period in late adolescence a cut-off value of 5 ng/mL is advocated for the diagnosis of persistent GHD and continuation of GH therapy because adolescents have higher GH levels than adults. In this study, there were 3 additional patients with peak GH level between 3-5 ng/mL in the isolated GHD group and none in the MPHD group. Therefore, no suggestion is available for patients in this gray zone. Furthermore, the prognosis of patients with a GH response of 5-10 ng/mL is not known. Therefore, it is important to keep in mind that clinical signs of GHD may occur later in life and the clinician must look for these manifestations in patients with a history of childhood GHD.³

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References

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IGFBP-3 Promoter Polymorphism Affects Response to GH Treatment for GH Deficiency

Growth responses to growth hormone (GH) therapy vary considerably among children with GH deficiency despite receiving standardized per kg body weight doses. Several clinical factors have been identified in influencing responsiveness to treatment,¹ but about half of the variation remains unexplained. These clinical factors only indirectly consider genetic traits, by including parental target heights.

Thus, Costalonga et al sought to examine the effects of an *insulin-like binding protein (IGFBP)-3* promoter polymorphism on growth velocity during the first year

of GH treatment in prepubertal children with severe GH deficiency. In twin studies, about 60% of the interindividual variability in circulating IGFBP-3 levels was found to be genetically determined.² A single nucleotide change 202 bp upstream of the transcription start site was found to affect IGFBP-3 promoter activity in vitro and in vivo; mean circulating IGFBP-3 levels in healthy adults were highest in those with AA genotype at the -202 position, less in AC and lowest in those with CC.

Costalonga et al studied 48 boys and 23 girls with severe GH deficiency (mean height z-score of -4.3 ± 1.4 SD,