Serum Insulin-Like Growth Factor-II (IGF-II) Levels in Patients with Acromegaly and Growth Hormone Deficiency: Correlation with IGF-I and IGF Binding Protein-3

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INSULIN-LIKE growth factor-I (IGF-I) and IGF-II are bound to the specific IGF-binding proteins (IGFBPs) in the circulation. Among the six IGFBPs so far characterized, IGFBP-3 is the most abundant. The measurement of IGF-I and IGFBP-3 levels is useful for the diagnosis of GH disorders, since both parameters are GH dependent, but the significance of IGF-II, which is less dependent on GH, remains to be determined. In the present study, we measured serum levels of IGF-II together with IGF-I and IGFBP-3 in normal subjects, acromegalic patients and GH deficiency in adults, and investigated the interrelationship among these parameters.

Subjects and Methods

Fifty normal subjects aged from 21 to 89 years, 32 patients with acromegaly (age: 24-64 yr) and 21 patients with GH deficiency (age: 22-68 yr) were included in the study. The acromegalic patients were subdivided into two groups, active and inactive, according to the clinical activities such as acral enlargement, excessive sweating, headache and arthralgia. GH deficiency was diagnosed by the inadequate GH responses to insulin-induced hypoglycemia (peak GH levels less than 3 ng/ml). All patients with GH deficiency were associated

with other pituitary hormone deficiencies and received adequate replacement therapy except GH.

Serum levels of IGF-II, IGF-I and IGFBP-3 were determined by specific immunoradiometric assays (IRMAs), as described previously [1]. Since IGFs were log-normally distributed, data were log-transformed to calculate the reference ranges (mean $\pm$ 2SD).

Results

In normal subjects, serum IGF-II levels were stable throughout adulthood, whereas serum levels of IGF-I and IGFBP-3 were decreased with age. In patients with active acromegaly, serum levels of IGF-I and IGFBP-3 were noticeably increased but IGF-II levels were within the reference range, as shown in Fig. 1. After successful therapy, IGF-I decreased to normal or low-normal levels and IGF-II remained normal. Almost all patients with GH deficiency had low levels of IGF-I. Serum levels of IGF-II and IGFBP-3 were lower than in normal subjects, but one-third of patients with GH deficiency had normal IGF-II and IGFBP-3.

There was a weak positive correlation between IGF-II and IGF-I levels in normal subjects and GH deficient patients. IGFBP-3 levels were best correlated with log IGF-I ($r=0.75$). IGF-II levels were correlated with IGFBP-3 in all subjects except active acromegaly ($r=0.86$). As shown in Fig. 2, the sum of IGF-II and IGF-I showed a strong positive correlation with IGFBP-3 levels ($r=0.88$). The calculated ratio of IGF-I to IGFBP-3 was not superior to IGF-I or IGFBP-3 alone to distinguish acrome-

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Fig. 1. Serum IGF-II levels in patients with active (■) and inactive (□) acromegaly and GH deficiency in adults (▲). Bars and boxes indicate the mean $\pm$ 2SD of normal subjects.

Fig. 2. Correlation between IGFBP-3 and the sum of IGF-I and IGF-II in normal subjects (●), patients with acromegaly (□), and GH deficiency in adults (△).

galy or GH deficiency from normal subjects in the present study.

Discussion

In the present study, IGF-II concentrations were measured by a newly developed IRMA using a non-extraction method. The serum levels were log-normally distributed, and the mean IGF-II values in normal adults were around 500 ng/ml, which were somewhat less than the values in radioimmunoassays (RIAs) previously reported [2-7]. The discrepancy may be partly caused by the different cross-reactivities of IGF related peptides and degraded fragments of IGF-II in various assays using different antibodies or by different IRMA and RIA methods.

Serum IGF-II levels were stable throughout adulthood, in contrast to the levels of IGF-I and IGFBP-3. Daughaday *et al.* [3] reported that serum IGF-II determined by radioreceptor assay was greater in adults more than 70 years of age, but we did not observe this phenomenon in our normal

subjects. Serum IGF-II levels were within the reference range in active and inactive acromegaly in accordance with others [2–4, 8] except one report [9]. We found that serum IGF-II levels were lower in patients with GH deficiency than in normal subjects, but considerable overlaps were observed. Other investigators [2, 4, 5] have reported better discrimination of GH deficiency from normal subjects, but Rosenfeld [6] and Asakawa [9] have reported similar findings to in ours in pediatric patients. Serum IGF-II levels were therefore only partially dependent on GH, and other factors which regulate IGF-II levels remain to be determined.

The sum of serum IGF-I and IGF-II levels correlated significantly with serum IGFBP-3 in all subjects. This has previously been demonstrated in healthy individuals [10]. The ratio of IGF-I to IGFBP-3 has been reported to reflect free IGF-I [11],

but we observed marked overlaps between acromegaly and normal subjects and the ratio of IGF-I to IGFBP-3 levels was not superior to IGF-I or IGFBP-3 alone in the present study. Serum IGF-II levels were correlated with IGFBP-3 in normal subjects and GH deficiency in adults. Simultaneous measurement of IGF-I, IGF-II and IGFBP-3 may provide further insights in understanding the pathophysiology of GH disorders.

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