Serum Insulin-Like Growth Factor II in 44 Patients with Non-Islet Cell Tumor Hypoglycemia

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Abstract. Serum insulin-like growth factor II (IGF-II) was characterized by radioimmunoassay and Western immunoblot in 44 patients with non-islet cell tumor hypoglycemia (NICTH). 31 of 44 patients with NICTH had big IGF-II in sera. When the presence of IGF-II in tumors from 20 patients was investigated, IGF-II in tumors was detected in 18 patients and these patients had big IGF-II in sera. In two patients whose tumors did not contain IGF-II, big IGF-II in sera was not detected. In six patients with IGF-II in tumors, hypoglycemia disappeared and the big IGF-II decreased after successful removal of the tumors. These data indicate that the big IGF-II could be related to hypoglycemia, and that the increased serum big IGF-II suggests IGF-II-producing NICTH. Serum IGF-II levels in 31 patients with big IGF-II were greater than those in 13 patients without it (Mean ± SEM: 723 ± 54 vs. 326 ± 31 ng/ml), but the elevated IGF-II levels were found in only 13 patients. Serum IGF-I levels were low in all patients with NICTH. In the 13 patients without big IGF-II, serum IGF-II levels were lower than those in the patients with big IGF-II, and serum IGF-I levels were also low. Serum IGF-II/IGF-I ratios in the patients with big IGF-II were elevated and greater than those in the patients without big IGF-II (35.0 ± 2.2 vs. 11.5 ± 2.4). The present data indicate that IGF-II-producing tumors are not rare in NICTH, and serum big IGF-II and IGF-II/IGF-I ratio are useful for screening patients with IGF-II-producing NICTH.

Key words: Insulin-like growth factor II (IGF-II), Hypoglycemia, Non-islet cell tumor hypoglycemia (NICTH)

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Serum IGF-I and IGF-II were measured by RIA using acid-ethanol extracted samples as reported previously [11, 12]. In these RIAs, the normal values for serum IGF-I and IGF-II in adults ranged from 88 to 240 ng/ml and from 374 to 804 ng/ml, respectively.

Western immunoblot analysis of IGF-II

Size heterogeneity of IGF-II in serum was investigated by Western immunoblot (WIB) according to the modified methods of Enjoh et al. [8]. Briefly, acid-ethanol extracted serum samples were electrophoresed on 16% SDS-acrylamide gel under non-reducing condition. The size fractioned proteins were electroblotted onto nitrocellulose sheet. The sheet was blocked with 5% (w/v) skim milk, and then incubated with anti-IGF-II antibody (Amano Pharmaceutical Co., Japan). After extensive washing, the sheet was incubated with horse radish peroxidase (HRP)-conjugated anti-mouse IgG, and then IGF-II-anti-IGF-II antibody complexes were detected with Enhanced Chemiluminescence (ECL) system (Amersham Co., Buckinghamshire, UK).

Results

Serum IGF-II by WIB

Serum IGF-II heterogeneity was analyzed by WIB (Fig. 2). In normal subjects, most of the IGF-II was detected at 7.5 kDa as an authentic size, but a minor form is 11 kDa IGF-II. In 31 of 44 patients with NICTH, most of the IGF-II was detected at 11-18 kDa, designated as big IGF-II, and a little 7.5 kDa IGF-II was detected. The clinical features of 31 patients with big IGF-II and 13 patients without big IGF-II are shown in Fig. 1.

The presence of IGF-II in tumor tissues from 20 of 44 patients was investigated by RIA, immunohistochemistry or Northern blot, and then IGF-II was detected in the tumors from 18 of 20 patients. Eighteen patients with IGF-II in tumors had big IGF-II in sera, but two patients without IGF-II in tumors did not have big IGF-II in sera. In six of 18 patients with IGF-II in tumor , hypoglycemia was disappeared and the big IGF-II decreased after successful removal of the tumors (Fig. 3).

Serum IGF-I and IGF-II levels

In the patients with NICTH with big IGF-II, serum IGF-II levels ranged from 294 to 1492 ng/ml.
ml with a mean of 723 ± 54 ng/ml (± SEM), and the elevated IGF-II levels were found in only 13 patients (Fig. 4). Serum IGF-I levels were low in all patients, with a mean of 22.2 ± 2.2 ng/ml. In the 13 patients with NICTH without big IGF-II, serum IGF-II levels ranged from 120 to 505 ng/ml with a mean of 326 ± 31 ng/ml, and serum IGF-I levels ranged from undetectable to 85 ng/ml with a mean of 41 ± 7 ng/ml (Fig. 4).

The serum IGF-II/IGF-I ratio was calculated in these patients (Fig. 5). In the patients with NICTH with big IGF-II, the IGF-II/IGF-I ratio ranged from 16.4 to 64.2 with a mean of 35.0 ± 2.2. These values were significantly higher than those for the patients with NICTH without big IGF-II, with GH deficiency, with acromegaly, and normal subjects (11.5 ± 2.4, 12.8 ± 1.9, 1.1 ± 0.3, 3.3 ± 0.2: Fig. 5).

**Discussion**

We measured serum big IGF-II in patients with NICTH, and found that 31 patients had big IGF-II in sera. When the presence of IGF-II in tumors from 20 patients with NICTH was investigated, IGF-II in tumor was detected in 18 patients and
these patients had big IGF-II in sera. In two patients whose tumors did not contain IGF-II, big IGF-II was not detected in sera. In six of 18 patients with IGF-II in tumor, hypoglycemia disappeared and the big IGF-II decreased after successful removal of the tumors. These data indicate that the big IGF-II could be related to hypoglycemia, and that the increased serum big IGF-II suggests IGF-II-producing NICTH. Therefore 13 patients with serum big IGF-II, in whose tumors the presence of IGF-II has been not investigated, were thought to have IGF-II producing NICTH. In these patients with IGF-II-producing NICTH, there are mesenchymal origin tumors, such as mesothelioma, leiomyosarcoma, histiocytoma, and fibrosarcoma, etc, but there are also other origin tumors, such as hepatocellular carcinoma and gastric cancer.

Serum IGF-II levels in the patients with big IGF-II were greater than those without big IGF-II, however, serum IGF-II levels were not elevated in all patients with NICTH with big IGF-II as reported previously [3–5]. Only 13 of 31 patients with big IGF-II had elevated serum IGF-II levels, and serum IGF-I levels were low in all patients with NICTH.

When IGF-II/IGF-I ratios in sera were calculated, they were high in the patients with big IGF-II, being more than 20 in 29 of 31 patients. The IGF-II/IGF-I ratios were less than 20 in 12 of 13 patients without big IGF-II. These data show that in the patients with IGF-II producing NICTH, serum IGF-II levels based on IGF-I levels are inappropriately elevated as suggested previously [13].

Our present data indicate that IGF-II producing tumors are not rare in the NICTH, and serum big IGF-II and IGF-II/IGF-I ratio are useful for screening the patients with IGF-II producing NICTH.

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