Severe Hypoglycemia Induced by IGF-II Producing Non-Islet Cell Tumor

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To the Editor Non-islet cell tumor hypoglycemia (NICTH) is a rare syndrome associated with the presence of slow-growing massive tumors of mesenchymal origin. In the tumor tissues of NICTH patients, normal O-linked glycosylation at Thr75 needed for the proper peptidase processing of pro-IGF-II is considered to be deficient. In normal human serum, pro-IGF-II accounts for 10-20% of the total IGF-II, whereas in the serum of patients with NICTH, 60-80% of the IGF-II present as pro-IGF-II. The binary complex of pro-IGF-II and IGFBP-3 cannot bind to an acid-labile subunit and increased bioavailability of IGF-II leads to its binding to the insulin receptor causing severe hypoglycemia in patients with NICTH.

A 30-year-old man manifested convulsion and was brought to our hospital by ambulance. He had suffered from malignant hemangiopericytoma for ten years and his tumor gradually spread to the thyroid, skull bone, vertebra, and liver in spite of combination therapies including surgical resection, tandem high-dose chemotherapy (1), and radiation. On physical examination on admission, he was 167 cm tall and weighed 59.4 kg and his conscious level was Glasgow Coma Scale 5. He demonstrated severe hypoglycemia, 20 mg/dl, and a large amount of glucose (150 g/day) was continuously administered; however he still manifested lower blood glucose levels ranging from 70 to 90 mg/dl. To discontinue the infusion of glucose, he was instructed to self-monitor his blood glucose levels, and encouraged to have 3 meals and 4 snacks a day. Under this condition, endocrinology examination revealed IRI 1.0 μU/ml, IGFBP-3 0.8 μg/ml (normal range: 1.9-3.89), IGF-I 48.9 ng/ml (67-318), IGF-II 1,336 ng/ml (546-1,260), GH 0.75 ng/ml (normal: 0.63), cortisol 15.7 mg/ml (4.5-21.1), and glucagon 119 pg/ml (70-160 pg/ml). Conventionally, the identification of pro-IGF-II required size-exclusion acid chromatography which has been considered to be the gold standard however it is very time consuming. Thus, we performed rapid method analysis of the pro-IGF-II, i.e. Tricine-SDS-PAGE analysis and Western blot with reproducible separation of proteins in the 5- to 20-kDa range (2). It clearly demonstrated that big IGF-II with -15 kDa was predominant in the present case and in NICTH patients with fibrosarcoma, while mature IGF-II with -7.5 kDa was predominant in healthy subjects. The patients with malignancies are frequently associated with hypoglycemia due to loss of appetite or massive glucose uptake into tumor tissues; however the presence of pro-IGF-II should be screened in patients with malignant tumors since the identification of pro-IGF-II leads us to consider specific therapies such as self-monitoring of blood glucose, or usage of hGH and glucocorticoids to avoid fatal hypoglycemia.

Case 1; Fibrosarcoma
Case 2; Present Case
CON1 and CON2; Healthy Control Subjects

Figure 1. Tricine-SDS-PAGE analysis and Western blot with IGF-II antibody.

References
