"Big IGF-II"-induced hypoglycemia secondary to gastric adenocarcinoma

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SUMMARY

Non-islet cell tumor-related hypoglycemia is a rare phenomenon. We report the case of a 63 year-old man admitted for hemiparesia and a capillary blood glucose of 20 mg/dL. The presence of an immature form of IGF-II that can mimic the effect of insulin, namely "big IGF-II", explained this patient's hypoglycaemia. A moderately differentiated adenocarcinoma of the cardia with metastatic extension to the stomach and the liver was demonstrated. Octreotide failed to control the hypoglycaemia, therefore prednisolone (2 mg/kg per day) and enteral feeding prevented new episodes of severe hypoglycaemia.

Key-words: IGF-II · Hypoglycaemia · Gastric adenocarcinoma · "Big IGF-II" · Insulin.

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RÉSUMÉ

Hypoglycémie induite par « Big IGF-II », secondaire à un adénocarcinome gastrique

Les tumeurs extrapancréatiques hypoglycémiantes sont rares. Nous rapportons le cas d'un patient âgé de 63 ans hospitalisé pour hémiparésie d'origine hypoglycémique (20 mg/dL), dont le facteur causal était un précurseur de haut poids moléculaire de l'IGF-II (la « Big IGF-II »), qui mime les effets de l'insuline. Un adénocarcinome moyennement différencié du cardia était mis en évidence, avec extension gastrique et métastases hépatiques. Un traitement par octréotide s'est avéré inefficace. L'association de prednisolone (2 mg/kg/jour) et d'une nutrition entérale a permis de prévenir la récidive d'hypoglycémies sévères.

Mots-clés : IGF-II · Hypoglycémie · Adénocarcinome gastrique · « Big IGF-II » · Insuline.

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Neoplasia is one of the most common causes of spontaneously occuring fasting hypoglycaemia. The mechanism by which islet-cell pancreatic tumors induce hypoglycaemia is straightforward as they have an autonomous secretion of insulin. On the other hand, the mechanism in which non-islet cell tumor induce hypoglycemia is only beginning to be understood, even if this condition was first described more than 70 years ago [1]. Secretion of an immature form of IGF-II named "big IGF-II" seems to play a central role in most of non-islet cell tumor induced hypoglycaemia (NICTIH) [2, 3]. We report the case of a patient in which hypoglycaemia was determined to be associated with a gastric tumor and the presence of serum "big IGF-II".

Case report

A 63 year-old man was admitted for a rapid onset of weakness of the right side. On admission, he had a right hemiparesia and a capillary blood glucose of 20 mg/dL. The neurological deficit resolved after the intravenous infusion of 30 % glucose. The patient reported a loss of weight, episodic epigastric pains and several episodes of dizziness during the previous month. He weighted 68 kg and was 164 cm in height. The liver was enlarged and irregular and there were firm adenopathies in both subclavicular areas. Despite continuous 10 % glucose infusion during the first day following admission, systematic venous glycemic control revealed 3 severe episodes of hypoglycaemia (13, 20 and 45 mg/dL) *(Fig 1)*. Serum insulin concentrations obtained concurrently were all 3 pmol/L (N 36-107). Plasma growth hormone was below 0.10 mUI/L (N 0.160-13) and insulin like growth factor-I (IGF-I) was 12 ng/mL (N 72-340). Western immunoblot analysis of serum IGF-II and its precursors was performed (Laboratoire d'explorations fonctionnelles endocriniennes, Hôpital Armand Trousseau, Paris, France), documenting an increased proportion of a high molecular weight protein (10 to 20 Kda) consistent with "big IGF-II". Gastrointestinal endoscopy with biopsies showed a moderately differentiated adenocarcinoma of the cardia, with extension to the stomach. Ultrasound examination of the abdomen showed a metastatic extension to the liver. Octreotide failed to control the hypoglycaemia, therefore prednisolone (2 mg/kg per day) and enteral feeding with a nasogastric tube were administered which prevented new episodes of severe hypoglycaemia *(Fig 1)*. Specific therapy of the tumor was not possible and the patient died 2 months after his admission.

Discussion

In this observation, severe fasting hypoglycaemia with clinical evidence of a disseminated malignancy suggested the presence of an underlying paraneoplastic syndrome. In this context, low plasma GH and IGF-I concentrations were consistent with inappropriate insulin secretion but insulinemia was found to be markedly decreased. The finding of "big IGF-II", an immature form of IGF-II that can mimic the effect of insulin, explained this patient's hypoglycaemia. IGF-I and II are two polypeptides synthesised by the liver

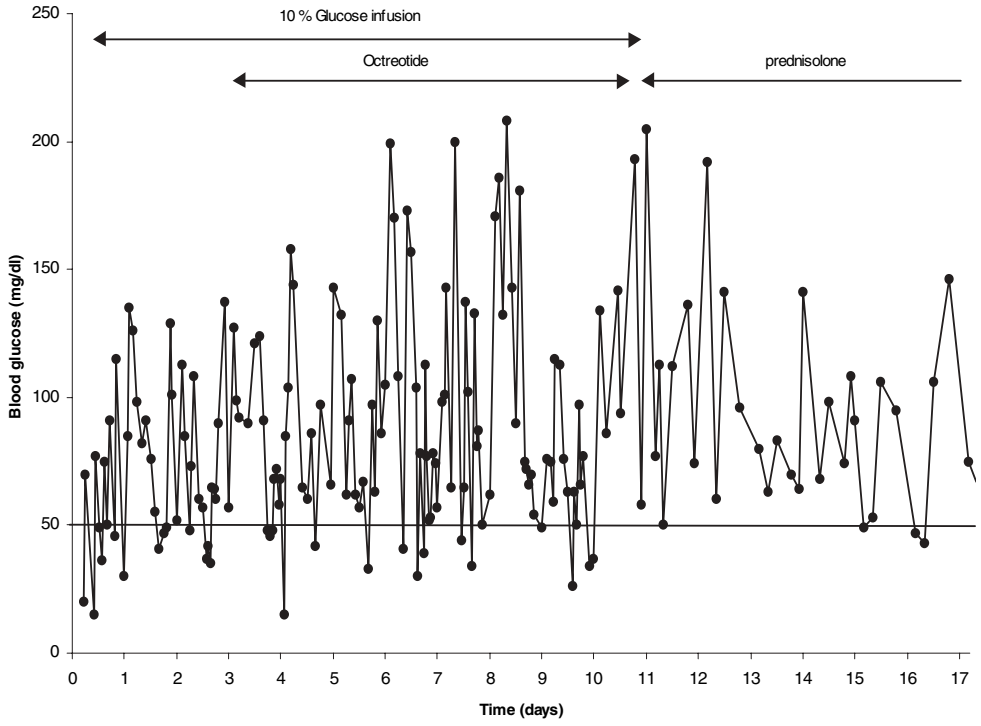

Figure 1
Changes of blood glucose with time in this case of "big IGF-II" —induced hypoglycemia. Corticosteroid therapy reduced significantly the occurrence of severe hypoglycemia.

which have structural homology with insulin. In healthy subjects, their main effect is induction of cell proliferation by linkage to their type I receptor. They have also a low affinity for insulin receptor but they do not take part in glucose regulation at their physiological concentrations. Compared to mature IGF-II, bioavailability of "big IGF-II" is markedly increased as it links to a smaller binding protein hence forming complexes that can cross the capillary barrier and activate the insulin receptor [4, 5]. While "big IGF-II" represents a small part of circulating IGF-II in normal human serum, it has been found to be increased in 27 out of 30 patients with NICTIH studied by Zapf *et al.* [3], and similar results have been shown by Hizuka *et al.* [6]. These data suggest that paraneoplastic secretion of "big IGF-II" is probably the key element explaining the mechanism of hypoglycemia in most cases of NICTIH.

Many tumors may be responsible for NICTIH, and they are usually from mesenchymatous [2], haematological, or epithelial origin. Among the latter, gastric adenocarcinomas, as in our observation, are uncommon since less than 20 cases have been reported to date [7]. Treatment for this tumors and concurrent liver metastases is often exclusively palliative. In most cases, hypoglycaemia occurs in patients for which the neoplasia has been already been diagnosed. However, as in the case of our patient, hypoglycemia may be the presenting feature. Prognosis is very poor and the majority of the patients die within three months after the onset of hypoglycaemia [7].

Efficient treatments preventing hypoglycaemias are, however mandatory since they seriously impair quality of life. In the case of our patient, glucose infusion and octreotide both proved to be ineffective but prednisolone with continuous enteral feeding prevented new episodes of severe hypoglycaemia. This inconstant effect of octreotide to control NICTIH has already been reported by others [8]. On the other hand, successful prevention of severe episode of hypoglycaemia by corticosteroids has been frequently described [8, 9]. Corticosteroids seem to have a specific beneficial effect on NICTIH-induced secretion of "big IGF-II" and the clinical signs associated with this paraneoplastic syndrome. In patient treated with corticosteroids, "big IGF-II" is decreased in the serum, and it seems that normal regulation of glycaemia is restored. Such a decrease was not monitored in our observation, but corticosteroids proved their clinical efficiency by preventing new episodes of severe hypoglycemia. Then, corticosteroids seem to be the treatment of choice for NICTIH due to "big IGF-II" secretion [10]. Use of growth hormone has also been reported to be efficient for the symptomatic treatment of NICTIH. As its mode of action is different from corticosteroids, their association when corticosteroids alone fail to avoid hypoglycaemia might be a logical approach.

It is important to stress the point that "big IGF-II" is not involved in all the cases of NICTIH. Other mechanisms potentially implicated in those remaining cases are probably various, including hepatic failure due to neoplastic liver invasion, paraneoplastic secretion of insulin [11], or glucose consumption by the tumor. This latter mechanism may have contributed to induce hypoglycemia in the case of our patient, but could not be demonstrated *in vivo*.

In conclusion, important progress have been performed during the past ten years in the understanding of the mechanism of NICTIH. "Big IGF-II" seems to be frequently involved in the occurrence of this paraneoplastic syndrome, as in the case of our patient. In the context of a neoplastic disease distinguishing hypoglycaemia linked to "big IGF-II" secretion from other causes of hypoglycaemia might have important therapeutic implication.

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