INSULIN AUTOIMMUNE SYNDROME: A RARE CAUSE OF HYPOGLYCAEMIA NOT TO BE OVERLOOKED

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SUMMARY - We report the case of a Caucasian patient with insulin autoimmune syndrome (IAS), defined as the association of hypoglycaemic attacks with insulin autoantibodies in individuals not previously treated with exogenous insulin. This rare syndrome (more than 200 published cases) has been reported mainly in Japan. Most affected patients present with other autoimmune disorders, most often Graves' disease. In most cases, insulin autoantibodies appear a few weeks after the beginning of treatment with a drug containing a sulphydryl group. A significant increase in insulin and C-peptide plasma concentrations and the presence of other antorgan antibodies are observed. The susceptibility haplotype is present in the Japanese population, which may account for the high frequency of IAS. Spontaneous remission is observed in 80% of cases, with cessation of hypoglycaemic attacks and disappearance of insulin autoantibodies some months after withdrawal of the drug. This rare cause of hypoglycaemia in Caucasian subjects should be considered in aetiological investigation of spontaneous hypoglycaemia.

Key-words: hypoglycemia, Graves' disease, insulin autoantibodies, caucasian, insulin autoimmune syndrome.

RÉSUMÉ - Hypoglycémie par auto-anticorps anti-insuline: une cause rare d’hypoglycémie à ne pas méconnaître

Nous rapportons le cas d’un patient caucasien présentant une hypoglycémie par auto-anticorps anti-insuline. Ce syndrome associe des épisodes hypoglycémiques et des anticorps anti-insuline chez des patients n’ayant jamais reçu d’insuline exogène. Ce syndrome est rare (un peu plus de 200 cas dans la littérature), la majorité des cas a été décrite dans la population japonaise. La plupart des patients sont atteints d’une pathologie auto-immune, la principale étant la maladie de Basedow. Les anticorps anti-insuline apparaissent dans les semaines qui suivent l’introduction d’un médicament dont la structure chimique comporte un groupement sulfydryle. Biologiquement, on observe une élévation, parfois très importante, de l’insulinémie, une élévation du peptide C, et la présence d’autres anticorps anti-organes. Un haplotype de susceptibilité a été mis en évidence dans la population japonaise, ce qui pourrait expliquer la fréquence élevée du syndrome dans cette population. L’évolution est favorable dans 80 % des cas après l’arrêt du traitement. Cette étiologie rare d’hypoglycémie mérite d’être rappelée eu égard aux difficultés diagnostiques et thérapeutiques que posent les hypoglycémies.

Mots-clés : hypoglycémie, maladie de Basedow, anticorps anti-insuline, caucasiens, syndrome d’auto-immunité anti-insuline.
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taneous hypoglycaemia is a clinical and biological disorder involving complex diagnostic and therapeutic issues. Among the multiple causes of hypoglycaemic attacks, insulin autoimmune syndrome (IAS) is rare. The first case was reported in 1970 by Hirata et al. [1]. Since then, more than 200 reports have been published in Japan, but only 28 cases in Caucasian patients in Europe and the USA [2,3]. A new case of IAS is reported here in a Caucasian patient with Graves’ disease.

# CASE REPORT

A 50-year-old male Moroccan patient was seen in our department for clinical hyperthyroidism, but declined treatment. Three years later, he was admitted after a 9 kg weight loss, with asthenia, severe tachycardia and palpitations. Physical examination disclosed a firm diffuse vascular goiter and exophthalmos. Serum free T4 (> 120 ng/mL, normal range 6-19) and free T3 levels (129 ng/mL, normal range 2-6) were elevated, whereas TSH was undetectable. Thyroglobulin antibodies were negative and thyroperoxidase antibodies weakly positive (1/100, normal range < 15), whereas TSH-receptor antibodies were elevated (57 U/L, normal < 15). Treatment with carbimazole (Néo-mercazole® 60 mg per day was started, together with ß-blocking agents. Two months later, the clinical and biological status was normal, and ß-blockers were stopped. Three months after beginning carbimazole therapy, the patient was admitted to the emergency department in a coma, with associated diffuse sweating, bradycardia (40 bpm) and hypothermia (35.3°C). Plasma glucose was 2.2 mmol/L. All symptoms resolved after intravenous glucose administration, and carbimazole was withdrawn. In the days preceding admission, two suspected less severe hypoglycaemic attacks had occurred. In spite of a diet containing large amounts of carbohydrates, four hypoglycaemic episodes were subsequently recorded in the hospital, with plasma glucose levels between 1.9 and 2.5 mmol/L. Free T3 and T4 levels were in the normal range, while TSH remained undetectable. During hypoglycaemia (2.2 mmol/L), plasma C-peptide concentrations were high (9.2 ng/mL, normal: 0.5-2.5), whereas plasma cortisol levels were normal (11 ug/100 ml, normal 8-15). Determination of plasma insulin levels by radioimmunoassay was impossible due to the presence of insulin autoantibodies (IAA). The patient’s HLA genotype was A24-B39-35 DR4-8. IAA, measured by radioimmunoassay (immunoprecipitation of moniodinated human insulin), were absent before carbimazole treatment (1.5%, normal < 1.5%). At the time of hypoglycaemic attacks, a high titre of IAA (68%) was observed. Antibody affinity for insulin and circulating immune complexes was not determined. A positive test for IAA 3 months after the start of carbimazole confirmed the role of the drug in precipitating an immune response against insulin. Propylthiouracil treatment was begun, and the hypoglycaemic attacks disappeared on the fourth day of treatment. The patient was lost to follow-up after being discharged and returning to Morocco.

# DISCUSSION

The first insulin autoimmune syndrome (IAS) was reported by Hirata et al. in 1970 [1]. Before that time, the presence of insulin antibodies was considered solely a result of immunisation from exogenous insulin. More than 200 cases of IAS have now been reported in the literature, mainly in Japan (244 cases) [2]. In Japanese patients, IAS is the third leading cause of spontaneous hypoglycaemic attacks. Caucasian subjects seem to be less prone than Japanese to IAS, as only 28 cases have been recorded in Europe and the USA [2, 3]. The age of onset is 60 to 70 years, except for young female patients with Graves’ disease, and the sex ratio is 1. In nearly 80% of cases, IAS is associated with other autoimmune disorders such as Graves’ disease (25%), rheumatoid arthritis, systemic lupus erythematosus, vasculitis and chronic hepatitis [4]. The role of drug-induced autoimmunisation has been suggested since drugs containing sulphhydryl groups (methimazole, carbimazole, penicillamine, captopril, ß-mercaptopropionyl glycine, glutathion, pyritinol and imipenem) were administered in 50% of cases 4 to 6 weeks before the onset of hypoglycaemic attacks [2-6]. The reported prevalence of IAA in patients treated with carbimazole ranges from 6.3 to 20%. The clinical diagnosis of IAS is based on the occurrence of hypoglycaemic attacks a few weeks after initiation of treatment. A large increase in plasma insulin levels revealed by radioimmunoassay is observed (more than 1,000 pmol/mL, reaching 150,000 pmol/mL in some cases). The structure of circulating insulin is normal. The majority of IAA are polyclonal, belonging to the IgG class. Two subtypes of antibodies are produced: those with low affinity and high binding capacity (associated with hypoglycemic attacks [7]) and those with high affinity and low binding capacity. A strong association between IAS and HLA DR4 has been evidenced in 96% of Japanese patients (HLA DR4 frequency is 43% in normal Japanese controls). Analysis of nucleotide sequences indicates that the haplotype of patients with IAS is DR B1 * 0406, DQ A1 * 0301 and DQ B1 * 0302 (present in all patients and in 14% of controls) [8]. The DR B1 * 0406 allele appears to play an important role in preventing insulin peptides to T cells [9]. Dissociation of insulin from the insulin-antibody complex is thought to result in increased free insulin plasma concentrations and hypoglycaemia during fasting. The disease
course is benign in the majority of cases, with spontaneous remission in 80% of patients 4 to 12 months after withdrawal of the drug. In some cases, a recurrence of IAS has been observed following reintroduction of the drug. Treatment by corticosteroids is required in some cases [10]. Paradoxically, IAA may disappear spontaneously despite continued carbimazole or methimazole treatment [5, 10].

In conclusion, IAS associates spontaneous hypoglycaemic attacks and IAA, is observed mainly in patients with other autoimmune disorders, and is rare in Caucasians. As aetiological investigation of spontaneous hypoglycaemia may be difficult and involve surgery, IAA should be systematically assessed to detect IAS.

REFERENCES