Autoimmune hypoglycemia syndrome associated with α lipoic acid consumption

Síndrome de hipoglucemia autoinmune asociado al consumo de ácido α lipoico

Dear Editor,

The insulin autoimmune syndrome (IAS) is a rare cause of endogenous hyperinsulinism, characterised by fasting hypoglycaemia, postprandial hypoglycaemia or both, by very high levels of insulin and by positive anti-insulin autoantibodies (IAA). It can be induced by certain drugs, especially those with sulfhydryl groups, which have been related to up to 50% of the cases. In particular, its onset can be triggered by the α lipoic acid (ALA), increasingly used during the last years as nutritional supplement.

The case of a Caucasian 55 year-old female referred for hypoglycaemia examination is presented. Allergy to iodinated contrast was the only relevant history; no use of habitual medication was reported. She had a 2-month case history characterised by adrenergic and neuroglycopenic symptoms, both in fasting and postprandial states, that resolved after food intake, and a 2 kg weight gain (weight 53 kg, body mass index [BMI] 21 kg/m²). The physical examination using devices was anodyne. The general laboratory tests showed blood sugar levels of 3.2 mmol/L (4.1–6.9) and haemoglobin (HbA)ic of 5.6%. A fasting test was performed and it was positive at 3 h with blood sugar levels of 2.4 mmol/L (4.1–6.9); insulinemia: 1.033 pmol/L (21–174); C peptide: 4.10 nmol/L (0.26–1.44); and cortisol 419 nmol/L (155–678). The determination of urine sulfonylurea was negative. IAA determination was done.

A treatment with fractionated diet and 200 g of iv glucose was established, with recurrence of hypoglycaemia and occasional postprandial hyperglycaemia episodes.

Complementary examinations were required to rule out insulinaemia as the most frequent cause of endogenous hyperinsulinism. Given her history, 3 bolus of 50 mg/day of prednisone i.v. were administered prior to the computed tomography with contrast, which was normal. The echoendoscopy described a 3 mm nodule in the pancreatic head, whose citological analysis (fine-needle aspiration [FNA]) was consistent with normal pancreas. Table 1 shows the results of the selective angiography with calcium stimulation. Finally, a diagnostic laparotomy was performed. Manual examination and intraoperative ultrasound scan of the pancreas were normal; thus, only an extended biopsy was performed. After the intervention, the blood sugar levels were normalised and gave place to the progressive withdrawal of i.v. glucose contribution.

The received results of the IAAs (RIA) were 85.8% (normal: <8.2%). In a new targeted history, ALA intake (200 mg/day) as nutritional supplement (to prevent hair loss) during 15 days was discovered. The histological result showed hyperplasia of the pancreatic islets affecting approximately 10% of them and with insulin predominant expression. At the moment of discharge, the patient did not show new episodes of hypoglycaemia and insulinemia was normalised. After one year, the IAA levels have decreased without reaching normalisation. Corticosteroids as preparation for the radiological techniques were the only immunomodulator treatment administered.

The IAS, first described by Hirata in 1970, is a rare cause of hypoglycaemia, except in Japan where it constitutes the third cause. The cases described in Caucasian population are scarce. It affects patients aged between 40 and 80 years old, with no difference in gender. It is associated to autoimmune diseases (related to HLA-DRB1*0406 and HLA-DRB1*0403) such as systemic lupus eritematosus (SLE), among others, and to the use of drugs with sulfhydryl groups (e.g., methimazole). The physiopathology is barely known; the hypothesis is that the activity reducing the sulfhydryl group causes the rupture of the insulin disulphide bridges, exposing it to the cells that carry the antigen. Hypoglycaemia is the consequence of the dissociation of insulin and the IAAs, which occurs asynchronously with blood sugar levels. Insulinemia is higher than expected for an insulinoma, generally over 1000 pmol/L. Little data has been reported about the histology of these cases, and they are about cells hyperplasia. In 80% of the cases, the symptoms are resolved in weeks. The treatment includes a diet fractionated in carbohydrates as first line, discontinuation of any medication associated to IAS and glucocorticoids (prednisone 30–60 mg/day). Plasmapheresis and other treatments have demonstrated different results.

The ALA is an antioxidant with sulfhydryl groups. In 2004, it was approved as nutritional supplement and it is widely used nowadays. Seventeen cases of IAS related to the ALA have been described in Japan, and recently 7 cases were reported in the Caucasian population. IAS was our definitive diagnosis considering the presence of hypoglycaemia with occasional episodes of postprandial hyperglycaemia, very high levels of insulinemia and positive IAAs, selective arteriography with increased levels.

Table 1 Serum insulin concentration during the selective intra-arterial stimulation with calcium.

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Baseline</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common hepatic</td>
<td>936</td>
<td>1058</td>
<td>1080</td>
<td>1041</td>
<td>1005</td>
</tr>
<tr>
<td>Gastroduodenal</td>
<td>1035</td>
<td>1041</td>
<td>976</td>
<td>1008</td>
<td>1040</td>
</tr>
<tr>
<td>Proximal splenic</td>
<td>1092</td>
<td>1168</td>
<td>1081</td>
<td>1059</td>
<td>1065</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>1042</td>
<td>1046</td>
<td>1019</td>
<td>1042</td>
<td>1066</td>
</tr>
</tbody>
</table>

of insulin in the entire gland without a gradient, histology with hyperplasia of the pancreatic islets and symptoms resolution after the administration of corticosteroids, in the context of previous administration of ALA. The application of the modified Karch and Lasagna causality algorithm allowed the categorisation of our case as possible IAS related to the administration of ALA.

It is the first case of IAS associated to the use of ALA in Spain. The use of ALA must be included in the habitual history of patients under examination for endogenous hyperinsulinism.

References


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Platypnea-orthodeoxia syndrome and Budd–Chiari syndrome: An unreported association

Síndrome de platypnea-orthodeoxia y síndrome de Budd-Chiari: una asociación inédita

Dear Editor,

The platypnea-orthodeoxia syndrome (POS) is a very rare disease characterised by the presence of dyspnea (platypnea) and arterial desaturation on standing position (orthodeoxia), which improves in the decubitus position. On the other hand, the Budd–Chiari syndrome (BCS) is a condition characterised by the obstruction of the hepatic venous outflow in the absence of right heart failure or constrictive pericarditis. Said obstruction may occur in the hepatic veins or suprahepatic inferior vena cava. When the obstruction is caused by a thrombosis, it is called primary BCS. If it is caused by a tumour, it is called secondary BCS.1

We presented the case of a 35-year-old female patient who, 2 years before, had been diagnosed with primary BCS during pregnancy (week 11), evidenced by ascites and dyspnoea. The hepatic Doppler scanning showed thrombosis of the right and left suprahepatic veins and reduced flow in the middle suprahepatic vein. Anticoagulation therapy was started with low-molecular-weight heparin, and the patient gave birth on week 38 through vaginal delivery using forceps. In the subsequent outpatient study, the patient was diagnosed with polycythaemia vera (Jak2+, typical bone marrow biopsy and normal karyotype). Therefore, anticoagulation therapy was indefinitely maintained with acenocumarol.

During the BCS progress control, a year after the diagnosis, there was still no flow in the right and left suprahepatic veins, and the middle suprahepatic vein presented a large venous vessel compatible with collateral circulation. The portal vein was normal and presented hepatopetal circulation (at a speed of 23 cm/s). The liver and kidney functions were normal, and the endoscopic test ruled out the presence of varicose veins.

The patient attended our practice because she had moderate-mild effort dyspnea, with predominance during orthostatism (and, in particular, in some positions, such as when leaning forward) and improving in the decubitus position (platypnea). It had no other related symptoms.

The physical examination revealed hepatomegaly of 2 finger breadths, without any other pathological findings. The baseline saturation in oxygen was normal. As to the complementary tests, the electrocardiogram, the cardiac stress test, the spirometry and the diffusion test were normal. A transthoracic echocardiogram revealed interauricular septal aneurysm with the presence of a permeable oval foramen (POF) with a right to left short circuit and high bubble load. The rest of the results were normal. Due to diagnostic suspicion, the cardiac stress test was repeated and the patient was specifically asked to lean forward during the test. In this way, she showed a sudden decrease in the oxygen saturation at maximum effort (up to a 78%) and a sudden decrease in the respiratory reserve from 70 (6 min in the Bruce protocol) to 48% at maximum effort.

The oval foramen was closed by means of a percutaneous catheter procedure using an Amplatzer cribiform device of 25 mm, with good results and no complications.

First described in 1949,2 the POS results from a short circuit of non-oxygenated blood from the right auricle to the left auricle through an opening in the interauricular septum. The POS is characterised by the presence of two components: on the one hand, an interauricular short circuit or shunt (as an oval foramen or auricular communication) or an intrapulmonary short circuit (as the hepato-pulmonary syndrome or pulmonary arteriovenous malformations).3 On the other hand, the syndrome requires a functional component that favours the right-left short circuit when the patient moves from the decubitus position to orthostatism. This could be a defect in the auricular septum or right auricle, which increases blood flow from the inferior vena cava through the auricular defect. In this regard, various related diseases have been described, such as pneumonectomy, pulmonary hypertension or pleural effusion.4,5

Though the POF is present in up to one third of the general population,6 it almost never has clinical manifestations. The most

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