



Case report

Potential cause-effect relationship between insulin autoimmune syndrome and alpha lipoic acid: Two case reports

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ABSTRACT

Objectives: Insulin autoimmune syndrome (IAS) or Hirata disease is a rare cause of autoimmune hypoglycemia with apparent high insulin levels and anti-insulin autoantibodies and was first described by Hirata in Japan in 1970. IAS cases are usually related to exposure to sulfhydryl-containing drugs, which stimulate the production of insulin autoantibodies. Among sulfhydryl-containing compounds, alpha lipoic acid (ALA) has recently emerged as a cause of IAS. After the first observations of ALA-induced IAS were reported in Japan in 2006, an increasing number of cases related to ALA administration have been described. An Italian group recently reported on six cases of IAS of which one was associated with HLA-DRB1*04:06 and the remaining five with HLA-DRB1*04:03. This suggests that the latter is potentially involved in the genetic susceptibility of people of European descent to IAS.

Methods: Here, we describe two new cases of IAS in women that were triggered by ALA.

Results: Both cases are associated with HLA-DRB1*04:03 and confirm the evidence that HLA-DRB1*04:03 rather than HLA-DRB1*04:06 is specifically related to IAS susceptibility in Europeans.

Conclusions: Case reports of ALA-induced hypoglycemic episodes highlight the need for greater care in prescribing ALA supplementation as well as the identification of specific and personalized therapeutic targets.

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Introduction

Insulin autoimmune syndrome (IAS) or Hirata disease is a rare cause of autoimmune hypoglycemia that is characterized by the occurrence of spontaneous hypoglycemic episodes, either fasting or postprandial, with apparent high insulin levels and anti-insulin autoantibodies in individuals with no prior exogenous insulin administration [1]. IAS was first reported by Hirata et al. [2] in

1970 in Japan and since then, more than 300 cases have been identified among Asians and IAS represents the third leading cause of spontaneous hypoglycemia in Japan [3]. On the contrary, only 58 cases have been described so far among non-Asian individuals [4].

The investigation into possible genetic causative markers has revealed a strong association between IAS and HLA-DR4 [5]. Indeed, the HLA type of 27 patients with IAS showed that DR4 was commonly expressed, but it was expressed only in 43% of healthy controls. Furthermore, analysis of the nucleotide sequences of DRB1, DQA1, and DQB1 genes showed that all patients expressed DRB1*04:06 [6]. This association has been subsequently confirmed for the HLA-DRB1*04:06 allele as well as HLA-DRB1*04:03 but at a lower level [7]. Moreover, IAS cases have also been observed to relate to exposure to sulfhydryl-containing drugs (i.e., thiamazole, methimazole, D-penicillamine, tiopronin, or glutathione) [8], which stimulate the production of insulin autoantibodies.

The mechanism that underlies the occurrence of hypoglycemia in IAS is still debated but sulfhydryl-containing compounds, through their reducing activity, have been hypothesized to mediate cleavage of disulfide bonds in the insulin molecule, which in turn

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Table 1
Case 1: Oral glucose tolerance test interrupted at 240 min due to symptomatic hypoglycemia

Parameters	min 0'	min 30'	min 60'	min 90'	min 120'	min 150'	min 180'	min 240'
Glucose (mg/dL)	48	135	197	204	197	160	66	24
Insulin (μIU/mL)	137	171	222	254	285	286	239	197
C-peptide (ng/mL)	2.7	5.8	9.3	7.8	8.7	11.3	7.4	3.4

Table 2
Case 1: 72-h fasting test

Parameters	Day1 h.00	Day1 h.6	Day1 h.12	Day1 h.18	Day2 h.00	Day2 h.6	Day2 h.12	Day2 h.18	Day3 h.00	Day3 h.12	Day3 h.18	Day3 h.24
Glucose (mg/dL)	79	72	73	59	73	71	64	50	73	73	60	40
Insulin (μIU/mL)	12.3	49.0	44.1	44.7	47.4	34.1	32.7	26.4	41.2	30.8	26.2	20.5
C-peptide (ng/mL)	1.6	2.5	2.1	2.1	2.1	2.0	1.7	1.4	2.2	1.5	1.3	1.2

Table 3
Case 2: Oral glucose tolerance test

Parameters	min 0'	min 30'	min 60'	min 90'	min 120'	min 180'
Glucose (mg/dL)	72	109	135	153	198	195
Insulin (μIU/mL)	>1500	>1500	>1500	>1500	>1500	>1500
C-peptide (ng/mL)	4.3	8	10.2	12.1	13.9	15.6

becomes more immunogenic [9]. Among sulfhydryl-containing compounds, alpha lipoic acid (ALA) recently emerged as a potential determinant of IAS [10].

After the first observations of ALA-induced IAS were reported in Japan in 2006 [10], an increasing number of cases that were related to ALA administration have been described [11,12] with a similar association with HLA-DRB1*04:06 and fewer with HLA-DRB1*04:03. An Italian group recently reported on six cases of IAS. Of these, one was associated with HLA-DRB1*04:06 and the remaining five with HLA-DRB1*04:03, which suggests that the latter is potentially involved in the genetic susceptibility of people of European descent to IAS. [13] Here, we describe two new cases of IAS in white women that were triggered by ALA and associated with HLA-DRB1*04:03.

Case 1

A 66-year-old white woman was referred for an evaluation of recurrent episodes of severe hypoglycemia, which had commenced a month earlier. She was overweight (body weight: 70 kg; height: 155 cm; body mass index [BMI]: 29.1 kg/m²) and had no personal history of major chronic diseases. She reported the classic symptoms of hypoglycemia: Sweating, hunger, palpitations, and tremors that occurred 2 h or 3 h after meals and during the night. These episodes were resolved with the administration of glucose. During a similar episode while she was first hospitalized (March 2016), her plasma blood glucose level was 28 mg/dL with fasting insulin levels of 600 μ IU/mL. We suspected an insulinoma and performed imaging studies including abdominal computed tomography, magnetic resonance, and positron emission tomography scans with ⁶⁸ gallium, which excluded abnormalities of the pancreas. The only pharmacologic therapy consisted of ramipril 5 mg/d for hypertension. Importantly, there was no history of alcohol abuse or diabetes and no previous exposure to diabetes medications.

One month after the first observation, we performed an oral glucose tolerance test (Table 1) and 72-h fasting test (Table 2) to exclude a diagnosis of reactive hypoglycemia. Both tests showed very high insulin levels with no concomitant C-peptide elevation and excluded the possibility of increased endogenous insulin secretion.

We further analyzed the patient's medical history and realized that she had been under treatment with ALA (600 mg/d) for muscle cramps until 1 wk before the first hospitalization (March 2016). A presumptive diagnosis of IAS was made and later confirmed by immunologic testing that revealed high, positive, anti-insulin antibodies (18.4 units/L; normal range <2.4 units/L). Therefore, we started therapy with prednisone (25 mg/d) with the gradual disappearance of hypoglycemic episodes as a result. Steroid therapy was progressively reduced and finally suspended after 4 mo.

Case 2

The second case concerns an 82-year-old white woman who lost consciousness during a hypoglycemic event and was admitted to the emergency room. Pharmacologic therapy consisted of bisoprolol 1.2 mg, irbesartan 150 mg, and aspirin 100 mg per day. Importantly, her weight was normal (body weight: 71 kg; height: 170 cm; BMI: 24.6 kg/m²) and she had no history of alcohol abuse or diabetes and no previous exposure to diabetes medications.

During the hospitalization, the patient presented with at least two spontaneous nocturnal hypoglycemic episodes and a blood sample was collected to dose glucose, insulin, C-peptide, and counter-regulatory hormone levels. Her insulin levels were found to be very high (>1500 μ IU/mL) and the patient underwent abdominal computed tomography, magnetic resonance, and endoscopic scans to exclude the possibility of an insulinoma.

Both the 300 min oral glucose tolerance test (Table 3) and fast-ing test (Table 4), which was suspended after 24 h due to a severe episode of hypoglycemia, showed markedly elevated insulin levels that were often >1500 μ IU/mL and typical of IAS. Furthermore, the patient was taking ALA (300 mg/d) to promote weight loss. The diagnosis of IAS was confirmed by the presence of high positive

Table 4
Case 2: Fasting test suspended after 24 h due to a severe episode of symptomatic hypoglycemia

Parameters	d 1, h 06	d 1, h 12	d 1, h 18	d 1, h 24
Glucose (mg/dL)	34	51	49	36
Insulin (μIU/mL)	>1500	257.2	212.9	186.8
C-peptide (ng/mL)	4.2	2.9	1.8	1.2

levels of anti-insulin autoantibodies (50.6 units/L; normal range <2.4 units/L) and the patient initiated therapy with prednisone 25 mg/d. After discharge, the patient was seen twice per month at our outpatient clinic and monitored with a continuous glucose monitoring device. However, after 30 d of treatment, she continued to present with hypoglycemia. Prednisone was administered at the same dosage for another month and then gradually reduced until suspension after 9 mo.

Both patients underwent a genetic evaluation for HLA and both were found to carry the HLA-DRB1*04:03 allele.

Methods

Serum insulin and C-peptide levels were measured with the Siemens ADVA CENTAUR XPTT immunoassay system through CLIA immunometric detection. The range of the standard curve of insulin assay is 0.5 μ IU/mL to 300 μ IU/mL but the reportable range of the ADVIA Centaur Insulin assay is 1 μ IU/mL to 1500 μ IU/mL. Samples with insulin levels >300 μ IU/mL were automatically diluted by the system with a dilution factor of up to 1:5 and results >1500 μ IU/mL are reported as >1500 μ IU/mL.

Discussion

In this report, we describe two new cases of IAS that were induced by ALA in European women who are both carriers of the HLA-DRB1*04:03 allele. The role of HLA-DRB1*04:06 and HLA-DRB1*04:03 in the predisposition of Asians for IAS is already well known. However, of all seven cases [14] that have been previously described in Italy, five were associated with HLA-DRB1*04:03.

Our findings confirm the evidence that HLA-DRB1*04:03 rather than HLA-DRB1*04:06, is specifically related to IAS susceptibility in Europeans. The HLA-DRB1*04:03 allele is common among Europeans including Italians (Italian allele frequency: 0.0160) [15,16]. HLA-DRB1*04:03 is closely related to HLA-DRB1*04:06 and they share a very similar nucleotide sequence, which differs only at a single nucleotide in codon 37. HLA-DRB1*04:03 has been suggested as an evolutionary predecessor of HLA-DRB1*04:06.

Limited evidence is available for the role of HLA-DRB1*04:03 and aside from IAS, HLA-DRB1*04:03 has also been implicated as a risk factor for oxcarbazepine-induced maculopapular eruption in the Chinese population [17].

The mechanism of interaction between HLA-DRB1*04:03 and ALA is still unknown and additional studies may be useful to clarify the potential causative effect of ALA supplementation on autoimmune hypoglycemia syndrome. However, ALA is potentially able to induce severe hypoglycemic events, at least in genetically predisposed people.

Approximately 20% of IAS cases to date among non-Asian individuals were in Italians, who represent a high prevalence of reports compared with other countries. We cannot exclude that this observation is due to a greater abuse of ALA prescription in our country and a better knowledge of this potential side effect of ALA among clinicians in Italy on the basis of previous case reports [13].

Despite the absence of an established treatment protocol, initial treatment with high-dose steroids is generally sufficient. However, in rare cases, other personalized therapies may be necessary (e.g., a new treatment protocol has been described recently for a case of IAS in a 59-year-old European man, consisting of a sequential therapy of immune-absorption followed by rituximab added to steroids) [18]. Considering that ALA does not require a medical prescription and is thought to have weight-loss properties, its consumption has grown in recent years and this trend may explain the increasing number of recent IAS cases. ALA is a liposoluble vitamin [19] and its oxidized and reduced forms have antioxidant potential [20,21].

Furthermore, ALA could also chelate metals and is reported to have an insulin-sensitizing effect. Few randomized controlled trials have investigated the potential insulin-sensitizing effect of ALA but with inconclusive results. An improvement in the metabolic clearance rate for glucose that was evaluated using a euglycemic hyperinsulinemic clamp has been reported in patients with type 2 diabetes who were treated with 600 mg, 1200 mg, or 1800 mg per day for 28 d [22]. A significant reduction in insulin resistance has been reported in patients with polycystic ovary syndrome when treated with ALA 400 mg/d [23]. Furthermore, although mouse studies seem to suggest a potential effect of ALA supplementation on the reduction of body weight and fat mass by decreasing food intake [24], conflicting data are available in humans. A recent meta-analysis, aimed to evaluate ALA efficacy as a supplementation for weight loss and showed a significant reduction in body weight and BMI in the ALA treatment groups compared with placebo but the greatest effect was achieved after short-term ALA supplementation compared with long-term interventions [25].

Interestingly, only three trials have reported on the side effects of ALA (itching, urticaria, and gastrointestinal disorders) but no hypoglycemic episodes were reported in the more than 11 randomized controlled trials that have been conducted with more than 500 subjects exposed to ALA supplementation.

Conclusions

It is interesting to note that ALA supplementation could exert a contrasting effect. While ALA is prescribed to potentiate the effect of insulin and reduce body weight, ALA also might determine an autoimmune syndrome and stimulate the production of circulating anti-insulin antibodies, which seem to limit the effect of endogenous insulin.

Case reports of ALA-induced hypoglycemic episodes impose the need for greater care in prescribing ALA supplementation as well as the identification of specific and personalized therapeutic targets. Furthermore, when investigating differential diagnoses of hypoglycemia, physicians must be mindful of possible supplement self-prescription and consider IAS when more specific causes of hypoglycemia have been excluded.

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