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Insulin autoimmune syndrome in an Argentine woman taking α-lipoic acid: A case report and review of the literature

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Abstract

Insulin autoimmune syndrome is an unusual cause of spontaneous hypoglycaemia in non-Asian populations. In the majority of cases, this syndrome appears a few weeks after the administration of drugs containing a sulfhydryl group. A strong association between this syndrome and HLA-DR4 has been shown. Only seven cases have been described in non-Asian patients. We report the first case of insulin autoimmune syndrome in an Argentine woman taking alfa-lipoic acid. She developed hypoglycaemic symptoms approximately 1 month after starting therapy. Blood sampling collected during an episode of symptomatic hypoglycaemia showed low blood glucose level (2.39 mmol/L), high level of serum insulin (1971.55 pmol/L), inappropriately high level of C-peptide (2.36 nmol/L) and high levels of insulin antibodies (274.78 IU/mL). HLA-DNA typing identified DRB1*04:03. Due to the widespread use of alfa-lipoic acid for its antioxidant properties, clinicians should be aware that it may trigger an autoimmune hypoglycaemia in people with a genetic predisposition.

Keywords

Insulin autoimmune syndrome, alfa-lipoic acid, hypoglycaemia, Hirata disease, antibodies

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Introduction

The Hirata disease, also known as insulin autoimmune syndrome (IAS), is an unusual cause of hypoglycaemia characterized by high serum levels of insulin and a significant increase of endogenous antibodies which bind insulin/proinsulin and/or insulin receptor.[1–3]

Described by Yukimasa Hirata in 1972,[4] IAS is the third commonest cause of spontaneous hypoglycaemia in Japan, after Insulinoma and extrapancreatic tumours.[5]

IAS is closely related with HLA-DR4. In the Japanese population, HLA DRB1*04:06 and DRB1*04:03 (at lower level) are the alleles most frequently found in this clinical pattern.[6]

Viral infections[7] and drugs composed of sulphur/sulfhydryl groups such as methimazole,[8] captopril, D-penicillamine, mercaptans, clopidogrel, imipenem, albumin and diltiazem have been considered as the potential factors inducing IAS.[9] In several cases, IAS has been described in patients affected by other autoimmune disorders, such as autoimmune thyroiditis, membrano-proliferative glomerulo-nephritis and rheumatoids arthritis.[10–13]

In 2003, at the Kyushu local meeting of the Japan Diabetes Society, Hashinaga T. et al. reported a clinical case of IAS due to an additional sulfhydryl drug defined α-lipoic acid (ALA). In the recent years, an increase in cases of ALA-induced IAS has been described. IAS related to ALA administration has been reported most frequently in Japanese and Koreans subjects. Recently, seven new cases have been described in Italian patients.

We report a case of IAS induced by ALA in an Argentine woman who referred to our Department.

Furthermore, we provide a literature review of all the cases of IAS due to ALA administration, in order to open a comprehensive overview of the characteristics of this unusual disease.

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Case

A 66-year-old female referred to the Emergency Room for malaise and sweating. Laboratory findings showed low blood glucose level (2.56 mmol/L). She was admitted in our Department to study deeply the cause of hypoglycaemia. Informed consent was obtained.

Her clinical anamnesis was negative. Recently, due to joint pain, she started therapy with ALA (800 mg/day) for 1 month and, after a suspension of 15 days, she further continued for 10 days. Two weeks before the admission in our hospital, she discontinued this therapy due to repeated episodes of hand tremor and hunger that appeared 3–4 h after a meal. Furthermore, these symptoms regressed after sugar ingestion.

There was no family history of autoimmune or endocrine disorders.

The body weight was 72.55 kg and height was 170 cm (Body Mass Index 25.1 kg/m^2). At admission, heart rate was 84/min and blood pressure 120/80 mmHg. The patient was conscious and oriented. Clinical chest and heart exams were negative. She had no thyroid goitre, acanthosis, skin tags or clinical and serological evidence of underlying autoimmune disease. Neurological findings were normal.

Laboratory values showed normal results except for blood glucose levels: 3.8 mmol/L (n.v. 4.0–5.9 mmol/L), high level of serum insulin: 1116.5 pmol/L (n.v. $<$ 174 pmol/L), inappropriately high level of C-peptide (1.81 nmol/L, n.v. 0.3–2.36). Table 1 shows laboratory data on admission.

An oral glucose tolerance test performed over 240 min showed basal glucose value of 3.88 mmol/L, a peak of 6.9 mmol/L at 120 min and a nadir of 2.33 mmol/L at 240 min.

Therefore, we performed enzyme immunoassay to obtain a quantitative determination of IgG autoantibodies to insulin in human serum (MediZym, Autoantibodies to Insulin enzyme-linked immunosorbent assay (ELISA) Assay Kit, MEDIPAN). High titre of insulin antibodies (271 U/mL, n.v. $<$ 0.4) had been detected.

We repeated blood sampling during a symptomatic episode of hypoglycaemia that confirmed the above-mentioned data: low blood glucose level (2.39 mmol/L), high levels of serum insulin (1971.55 pmol/L), inappropriately high levels of C-peptide (2.36 nmol/L) and high levels of insulin antibodies (274.78 IU/mL).

The 72-h fasting test was not performed due to the need for intravenous glucose support during the repeated and frequent hospital episodes of hypoglycaemia.

Abdominal computer tomography and Octreoscan scintigraphy excluded the presence of Insulinoma.

HLA-DNA typing identified DRB1*04:03.

Patient required continuous *iv* 5% dextrose for 10 days. No further episodes of hypoglycaemia occurred. A diet with fractionated meals, composed of high-fibre foods and poor or fast-acting carbohydrate, was prescribed.

Figure 1 shows blood glucose, insulin levels and antibodies levels during the hospitalization and follow-up.

Discussion

In most cases, IAS appears a few weeks after the administration of a drug containing sulfhydryl group.

The reducing activity of these compounds promotes the dissociation of the insulin S-S binding and exposes the insulin α chain to the antigen-presenting cells.[14]

The amino acid sequence Ile-Leu-Gln, contained in the insulin α chain, has a strong affinity for DRB1*04:06 molecule.[14] Another peptide localized from no.8 to no.17 of the insulin α chain (TSICSLYQLE) shows a high affinity with this molecule. This amino acid sequence is able to stimulate the T cells of DRB1*04:06-positive patients, leading to the synthesis of polyclonal insulin autoantibodies.[14,15]

In 2003, Hashinaga T. et al. reported an IAS clinical case due to an additional sulfhydryl drug, namely ALA.

ALA, also called thioctic acid, is a compound with a strong reductive effect.[16]

The antioxidant properties of α-lipoic acid play an essential role in the treatment of diabetic peripheral neuropathic pain.[17] It is well known that the overproduction of reactive oxygen species is a common factor in the pathogenesis of atherosclerosis, diabetes mellitus and hypertension.

Furthermore, ALA is widely used as a health supplement for dieting and antiaging. In the past 20 years, ALA is often used as a dietary supplement in Japan. In these years, several cases of IAS have been reported and, after methimazolo, ALA has been considered the main cause of this syndrome.[18] Table 2 shows a summary of ALA-induced IAS cases described from 2003 to May 2018.[13,18–23] The majority of cases reported in the table have been presented exclusively in scientific meetings. Overall, 27 cases of Hirata disease due to ALA administration has been documented: 18 in Japan, 7 in Italy and 2 in Korea. In 23 patients, HLA-DNA typing has been reported. A total of 13 of 17 Asiatic patients had the HLA-DRB1*04:06 allele compared with only 3 Asiatic patients with DRB1*04:03. All Caucasian patients were Italian, in six of those HLA-DRB1*04:03 was identified while HLA- DRB1*04:06 was isolated in two cases.

We describe the case of an Argentine woman presenting episodes of hypoglycaemia related to the ingestion of ALA. The association of hypoglycaemia with extremely high levels of serum insulin was indicative of IAS.

Laboratory test showed inappropriately high level of C-peptide. It may be related to the cross-reactivity between C-peptide and proinsulin which may be immunologically counted and reported as 'free C-peptide'.[1,24,25]

Although in the reported cases the syndrome occurs mainly with neuroglycopenic symptoms, our patient experienced adrenergic symptoms that occurred 2–3 h after a meal. As reported in the scientific literature, also in our patient the symptoms appeared more than a month after starting therapy and disappeared spontaneously after 1 month of drug withdrawal.

Table 1. Results of laboratory test on admission.

Analyte	Patient's value	Reference range
Red blood count ($\times 10^{6}$)	4.6	(3.5–5.2)
Haemoglobin (gr/dL)	13.4	(12–16)
Haematocrit (%)	41.3	(34.5–52)
White blood count (/mm^3)	9.830	(4.3–10.8)
Platelet count ($\times 10^{3}$)	335	(150–450)
Creatinine (μmol/L)	63.64	(48.62–97.24)
Blood urea nitrogen (mg/dL)	46	(15–50)
Uric acid (mg/dL)	3.7	(2.4–5.7)
Sodium (mEq/L)	140	(133–145)
Potassium (mEq/L)	4.8	(3.3–5.1)
Albumin (gr/L)	30	(34–48)
Aspartate aminotransferase (IU/L)	18	(6–24)
Alanine aminotransferase (IU/L)	35	(13–45)
γ-glutamyl transpeptidase (IU/L)	62	(5–55)
C-reactive protein (mg/L)	<0.100	(0–3)
Tissue transglutaminase antibodies (IgA; IU/mL)	2.02	(<9)
Deamidated gliadin peptide antibodies (IgG; IU)	<2.8	(<20)
Deamidated gliadin peptide antibodies (IgA; IU)	<5.2	(<20)
Anti-endomysial antibodies (IgG)	Negative	
Anti-endomysial antibodies (IgA)	Negative	
Antiadrenal antibodies	Negative	
Anti-TPO antibodies (kIU/L)	15	(0–35)
Anti-insulin antibodies (UI/mL)	271	(0–0.40)
Fasting plasma glucose (mmol/L)	3.8	(4–5.9)
Immunoreactive insulin (pmol/L)	1116.50	(21.52–143.5)
C-peptide (nmol/L)	1.81	(0.3–2.36)
HbA1c (mmol/mol)	39	(23–42)
Prolactin (nmol/L)	0.38	(0.122–1.27)
TSH (mIU/L)	3.13	(0.35–4.5)
ACTH (pmol/L)	5.08	(0–10.12)
i-PTH (pmol/L)	4.8	(1.49–7.64)
25-OH-Vitamin D (nmol/L)	61.4	(>74.88)
GH (μg/L)	2.0	(0.01–10)

TSH: thyroid-stimulating hormone; TPO: thyroperoxidase; ACTH: adrenocorticotrophic Hormone; i-PTH: intact-parathyroid hormone; GH: growth hormone; HbA1c: glycated haemoglobin.

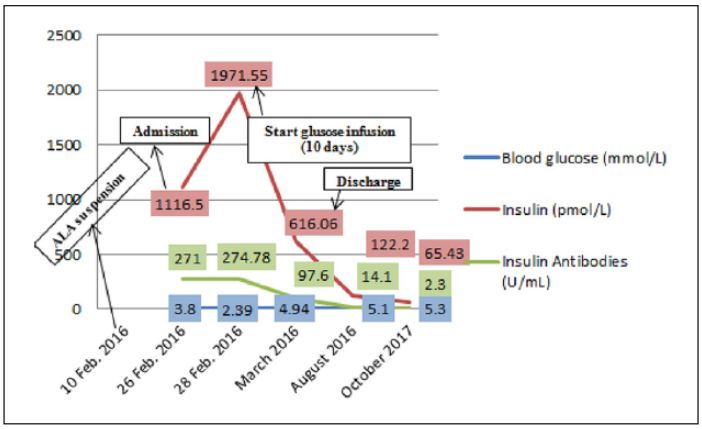

Figure 1. Blood glucose, serum insulin levels and antibodies titre during the hospitalization and follow-up period.

Table 2. α-lipoic acid-induced insulin autoimmune syndrome reported from 2003 to December 2016.

No.	Age	Sex	Insulin (pmol/L)	Country	Author	Year	HLA-DRB1
1	55	F	58.47	Japan	Hashinaga et al.	2003	0406
2	44	F	3860.15	Japan	Furukawa et al.	2006	0406 0901
3	67	F	5646.73	Japan	Kamiya et al.	2006	–
4	66	M	4735.5	Japan	Nishikawa et al.	2006	0406
5	49	F	1722↑	Japan	Takanashi et al.	2006	0406
6	34	F	2870	Japan	Yoshioka et al.	2006	0406
7	64	F	904	Japan	Kurashiki et al.	2006	DR4
8	32	F	3.860	Japan	Ishida et al.	2007	0406
9	34	F	3716.65	Japan	Nakajima et al.	2007	0406
10	55	M	18.16	Japan	Takeuchi et al.	2007	0406
11	36	F	464.94	Japan	Yoshida et al.	2007	–
12	35	M	13.95	Japan	Sasaki et al.	2007	0406
13	36	F	7139.13	Japan	Ogou et al.	2007	–
14	40	F	30.996	Japan	Kudo et al.	2007	0403
15	48	F	885.26	Japan	Matsui et al.	2007	0406
16	45	F	94.997	Japan	Yamada et al.	2007	0403
17	41	F	2047.03	Japan	Suzuki et al.	2007	–
18	32	F	17.15	Japan	Yoshihiko et al.	2007	0406
19	71	F	267.84	Korean	Chang et al.	2009	0406
20	70	F	408.98	Italian	Bresciani et al.	2011	0406
21	67	F	>7.175	Korean	Jeong et al.	2013	0406
22	75	M	1714.83	Italian	Gullo et al.	2014	0406
23	77	F	4018	Italian	Gullo et al.	2014	0403
24	53	M	2085.43	Italian	Gullo et al.	2014	0403
25	40	F	26561.85	Italian	Gullo et al.	2014	0403
26	70	F	1607.2	Italian	Gullo et al.	2014	0403
27	56	M	2001.83	Italian	Gullo et al.	2014	0403

Note: The majority of cases reported in the table have been presented exclusively in scientific meetings and were not published.

HLA-DNA typing identified DRB1*04:03. This finding confirms the implication of this allele in the genetic IAS predisposition also in not Asian population.

In our opinion, it is very suggestive that IAS related to ALA has been only described in the Asian population and in some Italian patients. The 'Allele Frequency Net Database' documented that HLADRB1*04:06 has a high prevalence in the Japanese population (allele frequency: 0.0339) while it is less common in Italy (allele frequency: 0.001).[26] HLADRB1*04:03 is common among Caucasians and the allele frequency in Italy and Argentine are, respectively, 0.01 and 0.014. Nevertheless, analysing the allele frequency distribution, in countries with a similar prevalence of HLADRB1*04:03 and common use of ALA (Germany, United States, etc.), no cases of Hirata disease related to ALA have been reported.

This epidemiological data is very interesting, although we have not clear evidence to explain it. In our opinion, there are some promoting or protective factors (genetic? environmental?) which can induce or swich off this autoimmune reaction. This aspect needs to be deeply investigated.

In our patient, hypoglycemic symptoms appeared more than a month after starting therapy and disappeared spontaneously after 1 month of drug withdrawal. After drug suspicion, the most effective therapy is usually the ingestion of several small amounts and avoiding meals with high glycaemic index carbohydrates. Otherwise, some patients required pharmacological intervention as alpha-glucosidase, corticosteroids, immunosuppressant and plasmapheresis. Alpha-glucosidase inhibitors, such as acarbose, delay the absorption of glucose, decreasing the hypersecretion of insulin.[27] Another possible therapy is corticosteroids.[8] Immunosuppressants and plasmapheresis may be used in not responsive patients.[18]

Conclusion

Nowadays, ALA therapy is widely used as a dietary and anti-aging supplement or as adjuvant therapy for symptomatic diabetic peripheral neuropathy; it is useful to know that, in patients with a genetic predisposition, this treatment could induce IAS. A prompt diagnosis is required and a targeted

diet should be applied; in some cases a pharmacological therapy in needed.

Declaration of conflicting interests

The author(s) declare no potential conflict of interest with respect to the research, authorship and publication of the article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases.

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Informed consent

Informed consent was obtained from the patient for anonymized patient information to be published in this article.

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