Mini Review

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Insulin autoimmune syndrome (Hirata's disease) in an Italian patient: a case report and review of the literature

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Abstract: We describe the case of a 54-year-old Caucasian Italian male experiencing episodes of hypoglycemia, occurring mainly after meals. He had never been exposed to insulin and was taking ramipril, flecainide and acetylsalicylic acid. An oral glucose tolerance test (OGTT) showed high blood glucose levels diagnostic for diabetes mellitus at 120 min and hypoglycemia with inappropriately high insulin levels at 240 min. The 72-h fasting test, abdominal computed tomography (CT) and positron emission tomography-CT were normal. Insulin autoantibodies were positive at high titers, prompting a diagnosis of insulin autoimmune syndrome (IAS). The patient was advised to take frequent, small meals and thus achieved a good control of his hypoglycemic symptoms. After 18 months of this dietary management, his insulin autoantibody levels decreased considerably but remained detectable. During an OGTT, his blood glucose levels at 120 min were now indicative of an impaired glucose tolerance rather than diabetes, and there was improvement in the glucose nadir. The patient had no other clinical or latent autoimmune diseases. Here we discuss the main features of IAS (also known as Hirata's disease) and review the cases of IAS reported in Italy to date.

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Introduction

In 1970, Hirata described a syndrome characterized by hypoglycemia and the presence of insulin autoantibodies (IAA) [1]. This rare insulin autoimmune syndrome (IAS) was thus called "Hirata's disease". It features hyperinsulinemic hypoglycemia, high serum levels of IAA and no history of exposure to exogenous insulin [2]. IAS is the third leading cause of hypoglycemia among Japanese people but is rare in Caucasians [2]. The Endocrine Society nonetheless included testing for IAA among the first-line assays to perform in non-diabetic adults with hypoglycemia [3], and this concept was reiterated thereafter [4]. Here, we describe the 12th case of IAS reported in Italy to date, along with the main features of IAS in this group of patients. Furthermore, we summarize the main characteristics of this syndrome worldwide.

Case report

A 54-year-old Caucasian male was referred to our hospital in June 2015 with frequent episodes of hypoglycemia. Since January 2015, he had experienced recurrent attacks of malaise, sweating, palpitations and tremors, both when fasting and after meals, with a documented hypoglycemia during these episodes (his plasma glucose levels were approximately 2.2–2.78 mmol/L). The symptoms disappeared after the ingestion of food. His body mass index (BMI) was within the normal range. He had a history of hypertension, an impaired fasting glucose tolerance and paroxysmal atrial fibrillation. He was taking perindopril/indapamide until January, then switched to ramipril, flecainide and acetylsalicylic acid. For a few

days immediately before the onset of his hypoglycemic symptoms, he had been taking two dietary supplements containing B group vitamins and chromium. The patient denied any use of exogenous insulin or oral hypoglycemic drugs. He was first examined elsewhere by another medical team, and in February 2015, he underwent a 180-min oral glucose tolerance test (OGTT) at another hospital. This showed a basal glucose level of 3.72 mmol/L, a maximum level of 16.21 mmol/L at 120 min and a nadir of 2.89 mmol/L at 90 min. A chemiluminescence microparticle immunoassay (Abbott Laboratories, Wiesbaden, Germany) revealed plasma insulin levels >4166.67 pmol/L (normal values [nv]: 18.75–72.22 pmol/L) at each time point during the OGTT, and C-peptide levels of 2.17 nmol/L at the baseline and 2.89 nmol/L at the glucose nadir (nv: 0.26–1.72 nmol/L). A tentative diagnosis of insulinoma prompted an abdominal computed tomography (CT) scan and a total body 68Ga-DOTANOC positron emission tomography (PET)-CT scan, both of which were negative. The patient was then referred to our Endocrine Unit in Padova. On physical examination, he was apparently healthy, with a BMI of 24.5. Laboratory findings, including thyroid and adrenal function, were all normal except for slightly increased chromogranin A levels, at 110 ng/L (nv: <84.7 ng/L). A 300-min OGTT test was carried out to investigate reactive hypoglycemia: the basal glucose level was 5.30 mmol/L, with a maximum level of 16.90 mmol/L at 90 min and a nadir of 2.60 mmol/L at 240 min. Plasma insulin ranged from a basal level of 243.06 pmol/L to a peak of 763.89 pmol/L at 120 min and 368.06 pmol/L at the glucose nadir (nv: 0–202.08 pmol/L), and C-peptide levels were 0.89 nmol/L at the baseline and 1.46 nmol/L at the glucose nadir (nv: 0.29–2.35 nmol/L); both measured at our institution by chemiluminescent immunometric assay (Siemens Automated Immunolite 2000, Siemens Medical Solutions Diagnostic, Malvern, PA, USA). Plasma glucose levels at 120 min of the OGTT were diagnostic for diabetes mellitus (Table 1). A test for IAA was judged to be necessary, and the serum was sent to FIRS Laboratories in Cardiff (UK).

While awaiting the result of the IAA assay, a 72-h fasting test was conducted, and no particular symptoms were noted. During this test, the plasma glucose nadir (3.57 mmol/L) occurred at the end of the fast and corresponded to inappropriately high insulin and C-peptide levels (145.8 pmol/L and 0.4 nmol/L, respectively; Table 2), whereas the concentration of proinsulin (2.40 pmol/L) was no higher than normal (nv: 0.70–8.30 pmol/L). The IAA test conducted by FIRS Laboratories revealed the IgG class of immunoglobulins at 483.20 IU/mL (nv: <0.4 IU/mL), using a radioimmunoassay (RIA) kit (Ria-IAA, from RSR Ltd, Cardiff, UK; www.rsrltd.com). The patient carried the human leukocyte antigen (HLA) allele DRB1*0403. Taken together, the clinical symptoms and laboratory findings were consistent with a case of IAS.

Following our investigations, the patient was discharged with the recommendation to eat frequent, small meals and to avoid simple sugars. He was prescribed no specific medication but continued to take ramipril, flecainide and acetylsalicylic acid for his previously diagnosed conditions. None of these drugs contain sulfhydryl groups, and the patient had taken no α-lipoic acid. The patient described here consequently represents a case of spontaneous IAS. During the subsequent follow-up, the hypoglycemic episodes became less and less frequent, ceasing altogether after a few months. At 6-month

Table 1: Results in 75-g oral glucose tolerance tests.

Time, min	Date: 29/05/2015			Date: 14/03/2016			Date: 30/11/2016		
	Insulin autoantibodies, 483.20 IU/mL[a]			Insulin autoantibodies, 115 IU/mL[a]			Insulin autoantibodies, 39 IU/mL[a]		
	Glucose, mmol/L[b]	Insulin, pmol/L[c]	C-peptide, nmol/L[d]	Glucose, mmol/L[b]	Insulin, pmol/L[c]	C-peptide, nmol/L[d]	Glucose, mmol/L[b]	Insulin, pmol/L[c]	C-peptide, nmol/L[d]
Basal	5.30	243.06	0.89	5.60	298.61	0.86	6.00	180.56	0.63
15	6.90	320.14	1.39	6.80	346.53	1.13	7.90	320.14	1.16
30	10.80	361.11	1.82	9.40	409.72	1.32	10.80	375.00	1.36
60	14.90	486.11	2.78	13.50	631.94	2.28	13.60	583.33	2.35
90	16.90	638.89	4.04	13.10	784.72	3.18	12.10	701.39	3.64
120	15.20	763.89	3.91	9.30	902.78	3.31	8.90	638.89	3.71
150	10.50	743.06	4.30	5.50	722.22	2.98	5.40	437.50	2.32
180	6.20	555.56	3.31	4.10	527.78	1.72	4.20	361.11	1.62
240	2.60	368.06	1.46	3.00	430.56	1.46	3.70	270.83	1.09
300	3.40	277.78	0.86	3.80	354.17	0.93	4.60	236.11	0.76

[a]Insulin Ab normal values (nv) <0.4 IU/mL; [b]glucose nv: 3.7–5.6 mmol/L; [c]insulin nv: 0–202.08 pmol/L; [d]C-peptide nv: 0.29–2.35 nmol/L.

Table 2: Seventy-two-hours fasting test.

Time, h	Glucose, mmol/L[a]	Insulin, pmol/L[b]	C-peptide, nmol/L[c]
8	5.9	270.8	0.9
14	4.6	201.4	0.7
20	4.53	201.4	0.6
26	4.54	201.4	0.7
32	4.10	201.4	0.7
40	3.9	187.5	0.4
46	3.65	152.8	0.5
52	3.86	173.6	0.5
58	3.6	173.6	0.5
64	3.9	173.6	0.4
70	3.57	145.8	0.4

[a]Glucose normal values (nv) 3.7–5.6 mmol/L; [b]Insulin nv: 0–202.08 pmol/L; [c]C-peptide nv: 0.29–2.35 nmol/L.

follow-up, the IAA assay was repeated, and the level had dropped to 120 IU/mL. A 300-min OGTT was repeated at 10 and 18 months after the diagnosis of IAS and showed an improved glucose tolerance and glycemia at 300 min (see Table 1). Further IAA tests at 10 and 18 months, performed in the same laboratory, showed a steady decrease in the autoantibody levels to 115 IU/mL and then 39 IU/mL. Tests were negative for all the other main organ- and non-organ-specific autoantibodies (to thyroid peroxidase, thyroglobulin, tissue transglutaminase [IgA and IgG], parietal cell, islet cell, glutamic acid decarboxylase, second islet autoantigen, adrenal cortex, 21-hydroxylase, side chain cleavage enzyme, 17-α hydroxylase, tryptophan hydroxylase, interferon omega, L-amino acid decarboxylase and anti-ENA). Although nuclear autoantibodies were detectable at a titer of 1:160 with homogeneous and mitotic fuse patterns, the patient showed no clinical signs of autoimmune rheumatic disease. Electrophoretic analysis of his serum proteins was normal, with no evidence of monoclonality.

Ethical conduct of research

Informed consent was obtained from the patient involved in this study.

Discussion

IAS worldwide

IAS is caused by the presence of a significant amount of endogenous IAA with a high binding avidity for insulin, triggered by infections and/or due to the presence of insulin receptor antibodies (type-B insulin resistance) [5]. Autoantibodies specifically against human insulin can be found in some subjects with established autoimmunity [6] and in patients with type 1 diabetes mellitus (especially in younger individuals) [7]. IAA have also been described in up to 2% of blood samples taken from healthy blood donors [8], but at low titers they have no pathological manifestations.

The mechanism behind the hypoglycemic episodes in IAS is probably related to the binding of IAA to endogenous insulin and the formation of insulin/autoantibody complexes, which – on dissociation – release biologically active insulin via a mechanism that depends not on blood glucose levels but on affinity constants of the bound IAA/insulin. During fasting, insulin concentrations are relatively low, and most autoantibody binding sites are unoccupied. When endogenous insulin levels increase (stimulated by food intake), the insulin molecules bind to the available sites on the IAA. The insulin/autoantibody complexes thus formed become dissociated in the postprandial phase (when the endogenous levels of insulin drop), leading to the release of biologically active unbound insulin and consequent hypoglycemia. This form of IAS is considered an autoimmune disease that would fit a novel concept of type VII hypersensitivity characterized by the presence of autoantibodies against circulating hormones or other circulating proteins [9, 10]. IAA also have the potential to interfere in some insulin, C-peptide and proinsulin immunoassays. A recent review on IAS [5] shed light on the pathophysiology and heterogeneity of endogenous antibodies and their clinical and analytical repercussions. In fact, antibodies have certain characteristics – such as intrinsic association/dissociation rate constants, titer/concentration and valency (high-affinity/low-capacity, or high-capacity/low-affinity) – that can determine a patient's symptoms and interfere with insulin, C-peptide and proinsulin laboratory tests.

Type-B insulin resistance is characterized by insulin receptor antibodies and usually causes insulin resistance associated with moderate-to-severe hyperglycemia. Patients manifest hypoglycemia, however, in 24% of cases, due to an agonistic effect of the antireceptor antibody. Hypoglycemia may be preceded by hyperglycemia, or it may be the first sign of the syndrome. Many patients have a fluctuating clinical course because of the simultaneous presence of agonistic and antagonistic insulin receptor antibodies, in variable titers and ratios [2, 5, 11].

Another possible mechanism behind IAS is the presence of a high-capacity, low-affinity paraprotein, capable of causing hypoglycemia associated with high plasma

insulin levels and relatively low C-peptide levels, and of delaying insulin clearance from the plasma insulin that remains available to bind its receptor due to the relatively weak affinity of the IgA for insulin [12].

In Japan, most patients with IAS had polyclonal IAA of the IgG class [13], whereas the IAA were monoclonal in more than half of the reported cases of IAS in non-Asian patients [2]. Although the most common IAA immunoglobulin class is IgG, cases of IgA and IgM IAA have been reported too [12, 14].

As far as triggers are concerned, in nearly half of the Caucasian patients described in the literature whose underlying causes and comorbidities were described, IAS had developed after exposure to drugs or other substances, especially those containing a sulfhydryl group (methimazole, penicillamine, α-lipoic acid, procainamide, hydralazine, etc.) [2], as seen in Japanese people [15]. It has been suggested that sulfhydryl groups are capable of binding and reducing sulfhydryl bonds that connect insulin chains A and B, making the self-antigen more immunogenic [3]. Drugs containing a sulfhydryl group may therefore cause or facilitate the development of IAA and IAS. In most non-Asian patients, however, the syndrome is associated with autoimmune or hematological diseases, and particularly with benign gammopathy and multiple myeloma – an association not often seen in Japanese patients [2]. Viral infections (e.g. mumps, rubella, chickenpox and measles) acting as super-antigens or molecular mimickers have also been reported as triggers [16]. It is only in a minority of Caucasian patients that IAS developed spontaneously, unassociated with any exposure to drugs, infections or autoimmune/hematological diseases [2, 17, 18]. When first reported, IAS was considered a rare condition, but its incidence has been increasing, possibly due to the widespread use of health supplements containing α-lipoic acid (also called thioctic acid) [19]. When taken orally and in the presence of NADH or NADPH, α-lipoic acid is reduced to dihydrolipoic acid, a compound containing a sulfhydryl group with a strong reducing activity [20]. α-Lipoic acid was used in the past to treat diabetic neuropathy. It was also used in Europe, the United States and Japan to manage acute necrotic encephalopathy, subacute necrotic encephalopathy and toxic hearing loss. Since 2004, α-lipoic acid has also been included in antiaging health supplements available in Japan and other countries [13, 21].

In Caucasian patients, IAS affects men and women equally, and it is more common in individuals over 40 years of age [2]. It is very rare in children, with one case in Brazil described in 2013, and only eight pediatric cases reported in the literature [22].

Early research on the genetic background of IAS indicated that it was associated with antigen DR4 of the HLA [23], but subsequent studies have shown that in Japanese patients it is associated with DRB1*0406 (odds ratio 56.6), and less frequently with DRB1*0403 and 0407 (odds ratios 1.6 and 1.0, respectively), whereas Caucasian patients more frequently carry HLA-DRB1*0403 [24].

From 1970 to 2009, there were 380 cases of IAS identified in Japan, where it is the third most common cause of hypoglycemia [15]. Outside Japan, IAS is very uncommon. From 1985 to 2013, there were 73 cases reported in China, and 64 of these patients had taken medication containing sulfhydryl compounds prior to the onset of their IAS symptoms [25]. Only one case has been reported in India to date, in a patient taking three drugs that contained sulfur and hydrogen atoms (pantoprazole, clopidogrel and torasemide) [26]. Among Caucasians individuals, after the first two cases described in Norway [27], another 70 cases have been reported in western European countries and North and South America [2, 17, 18, 20, 28–30].

IAS in Italy

Our patient is the 12th case of IAS to be reported in Italy so far (see Table 3 for details of the other 11 cases [17, 18, 20, 28–30]). All these patients were Caucasian, 11/12 of them adults (median age, 58 years; range, 40–78 years), and there was one child. Seven patients developed IAS after exposure to α-lipoic acid, in four (including the present case), the onset of IAS was spontaneous, and in one case, the cause was not reported. None of the cases of IAS in Italy were associated with methimazole therapy, probably because Graves' disease in Italian patients tends to be associated with DRB1*03, which differs from the HLA DRB1*0406 found in Japanese patients with Graves' disease [31]. HLA results were available for nine of the Italian patients with IAS: six were DRB1*0403, two were DRB1*0406 and one was DRB1*0407.

Six of the seven patients whose IAS related to α-lipoic acid exposure needed prednisone treatment (with diazoxide too in one case) for 20–100 days to improve their symptoms, whereas one patient only needed to eat more frequently. Out of four patients with spontaneous IAS, two required plasmapheresis (plus prednisone treatment in one), one needed prednisone and acarbose and only one (our case) needed no medication because his symptoms were well controlled by eating smaller, more frequent meals.

In the case described here, an OGTT performed after the onset of symptoms suggested overt diabetes,

Table 3: Literature revision of IAS cases reported in Italy so far.

Patients	Age, years	Sex	Cause	Insulin autoantibodies (IAA)	Insulin, pmol/L	HLA typing	History of DM or IGT/75-g OGTT result	Associated autoimmune diseases	Therapy	Ref.
1	Pediatric	M	Not specified	Not assayed	Not assayed	Not determined	Not specified	Not specified	Not specified	[28]
2	58	F	Spontaneous	Positive (62% ^{125}I Insulin binding)[a]	1680-2958[b]	Not determined	DM during OGTT when high IAA levels were present	None	Plasmapheresis and prednisone 75 mg/day tapered over 7 months to a manteinance dose of 12.5 mg/day	[17]
3	70	F	α-lipoic acid	210 arbitrary units[c]	395.83[d]	HLADRB1*0406	No history of DM/OGTT not described	Not reported	Prednisone (50 mg/day and diazoxide (300 mg/day) tapered over 30 days	[29]
4	40	F	Spontaneous	483.20 IU/mL[e]	157.64[f]	Not determined	IGT during OGTT when high IAA levels were found	Autoimmune thyroiditis	Plasmapheresis	[18]
5	75	M	α-lipoic acid	Positive (titers not specified)	34239[g]	HLADRB1*0406	No history of DM/OGTT not described	Rheumatoid arthritis	Oral prednisone 12.5 mg/day tapered over 60 days	[20]
6	77	F	α-lipoic acid	Positive (titers not specified)	55560[g]	HLADRB1*0403	History of DM/OGTT not described	None	Oral prednisone 25 mg/day tapered over 100 days	
7	53	M	α-lipoic acid	Positive (titers not specified)	367391[g]	HLADRB1*0403	No history of DM/OGTT not described	Membrano-proliferative gromerulonephritis	Oral prednisone 25 mg/day tapered over 100 days	
8	40	F	α-lipoic acid	Positive (titers not specified)	3702[g]	HLADRB1*0403	No history of DM/OGTT not described	None	Fractionated meals	
9	70	F	α-lipoic acid	Positive (titers not specified)	22224[g]	HLADRB1*0403	No history of DM/OGTT not described	Autoimmune thyroiditis	Oral prednisone, 12.5 mg/day tapered over 60 days	
10	56	M	α-lipoic acid	Positive (titers not specified)	15279[g]	HLADRB1*0403	No history of DM/OGTT not described	None	Oral prednisone, 12–5 mg/day tapered over 20 days	
11	78	F	Spontaneous	>40 IU/mL[h]	>6944.44[i]	HLADRB1*0407	No history of DM/OGTT not described	None	Prednisone 25 mg/day tapered over 60 days and acarbose	[30]
12	54	M	Spontaneous	369.80 IU/mL[e]	763.89[f]	HLADRB1*0403	DM during OGTT when high IAA levels were present, reversed to IGT with IAA levels decreased	None	Fractionated meals	Present case

[a]Results expressed as the percentage of total added radioactivity; [b]normal values (nv), not specified; [c]nv <5 arbitrary units; [d]nv: 41.67–187.50 pmol/L; [e]nv <0.4 IU/mL; [f]nv: 0–202.08 pmol/L; [g]nv: 13.89–138.89 pmol/L; [h]nv <2.40 IU/mL; [i]nv: 18.06–1736.11 pmol/L; DM, diabetes mellitus; IGT, impaired glucose tolerance.

whereas the same test repeated 10 months later (after the patient's IAA titers had dropped) revealed only an impaired glucose tolerance (Table 1). This goes to show that patients with IAS may paradoxically have hyperglycemia immediately after a meal or oral glucose challenge [17]. Insulin secreted in response to rising glucose levels after a meal is bound by IAA, giving rise to a reduction in the insulin available to bind to the receptors in target tissues, and thus impairing glucose metabolism. This hyperglycemic effect is dose dependent at IAA level. An impaired glucose tolerance and overt diabetes do not rule out a diagnosis of IAS, and high HbA_{1c} levels are common in patients with IAS [2]. A history of diabetes was reported in one of six patients described by Gullo et al. [20], and both Annese et al. [18] and Dozio et al. [17] reported an impaired glucose tolerance on OGTT in patients with high IAA titers (Table 3).

Our patient revealed no monoclonal pattern on electrophoretic analysis of the protein, but 5 of the 11 Italian patients with IAS tested for other autoimmune conditions were found to be affected (2 with chronic thyroiditis, 1 with rheumatoid arthritis, 1 with glomerulonephritis and 1 with high ANA titers) (see Table 3).

Present case report discussion

As mentioned previously, testing for insulin antibodies is mandatory in the differential diagnosis of hypoglycemia in non-diabetic patients. In fact, patients with IAS caused by IAA typically have high serum insulin levels, and their C-peptide and proinsulin concentrations may or may not be raised, depending on the characteristics of the antibodies causing the IAS and the reagents used in the immunoassays [5]. The presence of IAA can thus mimic a variety of scenarios, e.g. an insulinoma when insulin, C-peptide and proinsulin levels are high, or a self-administration of injectable insulin when insulin levels are high, but C-peptide and proinsulin levels are low. The patient may consequently be submitted to many useless and expensive tests, or even pancreatic surgery. In the early 1970s, partial pancreas excision surgery was performed in six patients with IAS misdiagnosed as cases of insulinoma: on histological examination, hyperplasia of pancreatic islets in the excised part of the pancreas was reported, with no sign of inflammation in the islets or peri-insular tissues [28, 32]. Our patient underwent a pointless abdominal CT, total body 68Ga-DOTANOC PET-CT and 72-h fasting test to rule out a hypothetical insulinoma and was examined by two medical teams before receiving a diagnosis of IAS. All these expensive and time-consuming tests would not have been performed if an IAA assay had been included among the first-line investigations. IAA assay as a first-line test is also fundamental to the proper interpretation of laboratory test findings when investigating hypoglycemia of undetermined origin in non-diabetic Caucasians. Unfortunately, it is not done at our laboratory, and the patient's sera had to be sent elsewhere. Other tests were performed to rule out an insulinoma while awaiting the result of the assay, although the fact that the patient's proinsulin levels were not high (2.4 pmol/L) should have raised the need of ruling out the presence of IAA at an early stage (according to the Endocrine Society Guidelines, proinsulin levels above 5 pmol/L are suspicious for endogenous insulin production) [3]. Measuring insulin with two different commercial kits is not always enough to reveal IAA interference, as our case report shows. In efforts to rule out the presence of IAA, it is also important to hear in mind their heterogeneity: although they are usually IgG class immunoglobulins, IAA can also belong to other classes, but commercially available kits can often only identify the IgG class (as in the case of the two-step RIA for the quantitative determination of IAA that we used). To avoid misleading results, it is of paramount importance for the initial IAA test used to be able to detect all immunoglobulin classes and subclasses [4]. Polyethylene glycol can precipitate all immunoglobulin IAA, and it is an inexpensive procedure within the capabilities of any clinical laboratory, so it should always be adopted, possibly followed by the identification of the specific class of IAA. In some cases of hypoglycemia of unexplained origin, with normal or elevated insulin and C-peptide levels, the presence of insulin receptor antibodies should be taken into consideration too.

In conclusion, autoimmune forms of hypoglycemia are rare among Caucasians but should be taken into consideration in the setting of unsuppressed insulin levels. The importance of testing for IAA in adult patients with hypoglycemia without diabetes mellitus has also been underscored in Endocrine Society Clinical Practice Guidelines [3].

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