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A novel atypical presentation of insulin autoimmune syndrome (Hirata's disease) in a child

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Abstract

Insulin autoimmune syndrome (IAS) or Hirata's disease is a rare cause of hyperinsulinemic hypoglycemia. We report the case of a child with a mild, atypical presentation of IAS. A previously healthy girl, aged 7 years old, developed non-ketotic fasting hypoglycemia during treatment for pneumonia. Laboratory evaluation during hypoglycemia showed the following results: serum glucose, 32 mg/dL (1.8 mmol/L); insulin, 5.6 μ IU/mL (38.9 pmol/L); C-peptide, 1.4 ng/mL (0.47 nmol/L); antiinsulin antibody, 6.2% (normal, < 2.4%); absence of ketonuria; and positive glucagon stimulation test result. Search for mutation in genes *ABCC8*, *KCNJ11*, *GLUD1* and *MEN1* was negative. Human leukocyte antigen (HLA) typing was *HLA-DRB1*1104*. Computed tomography scan of the abdomen showed a normal result. The patient evolved with spontaneous resolution of the hypoglycemia, within 30 days, with normalization of serum anti-insulin titers. The serum levels of insulin and anti-insulin antibodies in the patient of this report were not extremely high as previously reported. This novel, mild, or forme fruste presentation of IAS expands the previously reported spectrum of this disease.

Keywords

children; Hirata's disease; hyperinsulinism; hypoglycemia; insulin autoimmune syndrome

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Contribution of each author for the writing of the paper: CA and JC participated in the conception, design and data acquisition; wrote the initial the draft; and revised the final version. DDL, KS and CS and SE tested the *ABCC8*, *KCNJ11*, *GLUD1* and *MEN1* mutations and contributed to the final version.

Introduction

Insulin autoimmune syndrome (IAS) or Hirata's disease was described in 1979 in Japan (1). The diagnostic criteria for IAS are spontaneous hypoglycemia, elevated insulin, presence of anti-insulin antibodies and absence of prior use of exogenous insulin (1, 2). A differential diagnosis of autoimmune hypoglycemia is the one resulting from autoantibodies to the insulin receptor. IAS is the third leading cause of hypoglycemia in Japan, being 10–30 times more common among Asians (1, 3–5). This disorder is much more common in adults than in children, with only eight reported cases in children (5–9). Most patients were female, with the peak onset from 60 to 69 years of age (5). Given the rarity of this syndrome outside of Asia as well as in children, the present report aims to describe the case of a child with a novel, mild, atypical or form frusta presentation of IAS.

Case report

A 7-year-old girl developed non-ketotic fasting hypoglycemia during treatment for pneumonia with ceftriaxone and oxacillin. The initial clinical manifestation was seizure with serum glucose of 32 mg/dL (1.8 mmol/L) several hours into the course of her treatment. There was no report of head trauma, central nervous system infection, insulin treatment, family history of hypoglycemia or consanguinity between parents. There was no prior history of hypoglycemia. Birth and neonatal history were normal, and the child had normal neurodevelopmental milestones.

During hospitalization, the hypoglycemic episodes recurred when the intravenous glucose intake (average: 10–12 mg/kg per min), used to supplement the oral diet, was inadvertently interrupted.

Complete blood cell count; levels of blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, calcium, phosphorus, alkaline phosphatase, magnesium, sodium, potassium, chloride and uric acid; and results of computed tomography scan of the skull and abdomen and that of urinary tract ultrasound scan were normal. Laboratory evaluation at the time of hypoglycemia [32 mg/dL (1.8 mmol/L)] was remarkable for a non-suppressed plasma insulin concentration of 5.6 μ IU/mL (8.9 pmol/L), anti-insulin antibodies of 6.2% (normal, < 2.4), absence of ketonuria and an inappropriate glycemic response to glucagon (serum glucose increased by 76 mg/dL or 4.2 mmol/L), all compatible with the diagnosis of hyperinsulinism. A repeat hormonal evaluation in the presence of serum blood glucose levels of 10 mg/dL (0.56 mmol/L) showed the following results: insulin, 4.0 μ IU/mL (6.3 pmol/L); C-peptide, 1.4 ng/mL (0.46 nmol/L); anti-insulin antibodies, 5.1% (normal, < 2.4%); and adequate levels of free thyroxine, thyroidstimulating hormone, growth hormone, insulin-like growth factor 1 (IGF-1) and serum cortisol (Table 1).

Mutation screening for the most common causes of hyperinsulinism (*ABCC8*, *KCNJ11*, *GLUD1*) and insulinomas (*MEN1*) was negative (10). High-resolution *HLA-DRB1* typing revealed a *HLA-DRB1*1104* genotype.

Repeat analysis of anti-insulin antibodies, 16 and 37 days after the initial testing, showed a reduction of the values to 2.1% and 1.0%, respectively, which were temporally associated with normalization of glycemia. Interestingly, during this interval of time, therapy with steroids (hydrocortisone: 8 mg/kg per day, IV, q6h, for 7 days) was started due to bronchospasm and a severe urticarial allergic reaction.

After 62 days of hospitalization, the patient died of multiple organ dysfunction secondary to sepsis. Autopsy study was not done.

Discussion

Insulin autoimmune syndrome (IAS) is a rare disease, being even rarer in children, with only eight reported cases so far (Table 2). The mechanism of hypoglycemia in IAS is not fully known (2). It is assumed that two mechanisms are involved. Initially, in the immediate postprandial period, the auto-antibody binds immediately to insulin, and, subsequently, insulin dissociates from the complex with anti-insulin antibodies, causing hypoglycemia (2).

Insulin levels in IAS are usually very high (5), presumably a consequence of anti-insulin antibodies that interfere with insulin radioimmunoassay (11, 12). Although our patient had normal serum levels of insulin and C-peptide, both were inappropriately elevated in the presence of hypoglycemia, confirming the diagnosis of hyperinsulinemic hypoglycemia. The presentation at 7 years of age in a previously healthy child ruled out congenital forms of hyperinsulinemic hypoglycemia. In addition, genetic screening for mutations in the genes more commonly associated with congenital hyperinsulinemic hypoglycemia was negative. From the acquired forms of hyperinsulinemic hypoglycemia, an insulinoma was ruled out by negative imaging studies and by the spontaneous resolution of the hypoglycemia. Sequencing analysis of MEN1 was also negative.

In Japan, half of the patients report use of medications, 90% of which belong to drugs containing asulphydryl group (2, 5). The main medications associated with IAS are methimazole, glutathione, captopril, corticosteroids, interferon- α , α lipoic acid, imipenem and penicillin G (11). Recently, Gomez Cruz et al. (11) described a methimazole-induced insulin autoimmune syndrome in an African-American adolescent male. None of the drugs used by the patient of this report belongs to those associated with IAS.

IAS has a pattern of polyclonal anti-insulin antibodies in patients of East Asian countries, while Caucasian patients have a higher prevalence of monoclonal anti-insulin antibodies based on affinity curves with human insulin and the presence of solitary light chain (5). It was not possible to determine whether the pattern of anti-insulin antibodies found in our patient was mono- or polyclonal. Although our study did not characterize whether the insulin antibodies were monoclonal or polyclonal, there was no consensus as to which type was more prevalent.

The Japanese patients with IAS in whom human leukocyte antigen (HLA) haplotyping was performed have the following alleles *DRB1**0406, *DQA1**0301 and *DQB1**0302 (1). According to Nasu et al. (2), the alleles associated with increased susceptibility to IAS were *DRB1**0403, *DRB1**0406, *DRB1**0407 and *DR9*. Our patient was homozygous for

*DRB1*1104* which has not been reported to be a susceptible allele (12, 13). As this is the first Brazilian report with HLA description, we do not know which *HLA* genes are associated with the development of this disease in this population. We found two reports of IAS in Brazil, both in adults. Moreira et al. (12) described the case of a 56-year-old man who developed persistent hyperinsulinemic hypoglycemia with elevated C-peptide and antiinsulin antibodies, and Paiva et al. (14) reported on the case of a 55-year-old man. HLA haplotyping was not performed in these patients.

The duration of hypoglycemia in IAS is relatively short. Hirata and Uchigata (1) reported that most of the cases of hypoglycemia lasted less than 1 month. Spontaneous remission occurred in 82% of patients, in the same way as occurred with our patient. Interestingly, this coincided with the addition of steroids to her treatment regimen. The clinical improvement of the hypoglycemia was associated with decreased antibody titers, suggesting that the steroids may have ameliorated the autoimmune process. Others have reported the use of corticosteroids, as well as of plasmapheresis and immunosuppressants to treat IAS (12). A diet consisting of several light meals per day, avoiding simple sugars, is recommended (12).

Since there are no specific diagnostic tests to unequivocally confirm IAS, the clinical and laboratory data presented in this report are highly suggestive of a novel, mild, atypical presentation of IAS presenting with serum insulin levels not excessively high as previously reported, which is supported by spontaneous remission and absence of other known causes of hyperinsulinemic hypoglycemia. This finding suggests that the clinical spectrum of IAS seems to be more heterogeneous than previously assumed.

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Table 1

Endocrine and genetic evaluation

Laboratory evaluation	Days of follow-up				Reference range (SI units)
	Day 1	Day 7	Day 16	Day 33	
Fasting glycemia	32 (1.8)	10 (0.56)	77 (4.3)	84 (4.7)	70-99 mg/dL (3.9-5.5 mmol/L)
Insulin	5.6 (38.9)	4.0 (27.7)			0.9-6.1 µU/mL (6.25-42.3 pmol/L)
C-Peptide		2.4 (0.89)			0.9-4.8 ng/mL (0.3-1.6)
Anti-insulin antibodies	6.2	5.1	2.1	1.0	<2.4%
Free T4		0.89 (11.4)			0.83-1.73 ng/dL (10.6-18.8 pmol/L)
TSH		2.47 (2.47)			0.45-4.47 µU/mL (0.45-4.47 mIU/L)
IGF-I		237 (237)			57-315 ng/dL (57-315 µg/L)
Cortisol (0800 h)		19.25 (538)			6.7-22.6 µg/dL (184-623 nmol/L)
Intact PTH			30.9 (3.25)		9.5-63.8 pg/mL (1.0-6.7 pmol/L)
Total calcium			8.48 (2.12)		8.4-10 mg/dL (2.1-2.5 mmol/L)
HLA			<i>DRB1*1104</i>		
Mutation screening for the coding exons of <i>ABCC8</i> , <i>KCNJ11</i> , <i>GLUD1</i> , <i>MEN1</i>			Negative		

Hydrocortisone, 8 mg/kg per day, IV, q6h, was added to the treatment between days 14 and 21 to treat a severe allergic reaction.

TSH, Thyroid-stimulating hormone; PTH, parathyroid hormone.

Table 2

Pediatric reported cases of insulin autoimmune syndrome in children and adolescents.

References	Age, years	Gender	Underlying disease process	Serum insulin ^a	Anti-insulin antibody
Present report	7	Female	Pneumonia	5.6 µU/mL (1.9-23)	6.1% (<2.4)
Cited by Uchigata and Hirata (5)	11	Female	Hashimoto's thyroiditis	?	?
Cited by Uchigata and Hirata (5)	5	Male	Vasculitis	?	?
Cited by Uchigata and Hirata (5)	?	?	Pulmonary tuberculosis	?	?
Meschi et al. (8)	5	Male	Celiac disease	10.72 pmol/L (<25)	40% (<5%)
Rovira et al. (7)	4	Male	-	1175 µU/mL (1.9-23)	Positive
Goldman et al. (6)	0.8	Male	-	>1000 µU/mL (1.9-23)	Positive
Gomez Cruz et al. (11)	16	Male	Graves' disease	438 pmol/L (7.1-150.6)	5.7 nmol/L (0.0-0.02)

^aWhen the patients were hypoglycemic.