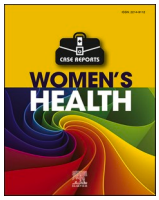
Case Reports in Women's Health 43 (2024) e00644

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh



Clinical and molecular evaluation of insulin autoimmune syndrome in a woman with Graves' disease who subsequently became pregnant: A case report

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ARTICLE INFO

Keywords:
Autoimmune hypoglycemia
Graves' disease
Insulin autoimmune syndrome
Hirata's disease
Pregnancy

ABSTRACT

Insulin autoimmune syndrome or Hirata's disease is a rare condition characterized by hypoglycemia associated with endogenous autoimmune hyperinsulinism. This report concerns the case of a 28-year-old Latin American woman with Graves' disease who developed insulin autoimmune syndrome and then subsequently became pregnant. She displayed symptoms related to severe hypoglycemia due to hyperinsulinemia, elevated C-peptide, and anti-insulin antibodies. Prior to pregnancy she was treated with corticosteroids and had ablative treatment with iodine-131. During follow-up of both conditions, the patient became pregnant, and clinically and biochemically hyperthyroid, for which total thyroidectomy was performed during the second trimester of pregnancy. Anti-insulin antibodies, blood glucose, and C-peptide remained normal throughout pregnancy. At 40 weeks of gestation she gave birth to a healthy female newborn with normal blood glucose values. Molecular genetic analysis determined the following genotypes: HLA-DRB1*03:01 / *HLA-DRB1*04:01 in the mother; and HLA-DRB1*04:01 / *HLA-DRB1*08:02 in the daughter. Because some HLA-DRB1*04 alleles are associated with susceptibility to insulin autoimmune syndrome induced by environmental factors, the patient was advised regarding the future use of drugs with a sulfhydryl group and possible triggering factors for insulin autoimmune syndrome. At 6-month follow-up the daughter presented normal growth and development, as well as normal plasma glucose values, and this remained the case at five-year follow-up.

1. Introduction

Insulin autoimmune syndrome (IAS) or Hirata's disease is a rare endocrine disorder characterized by repeated episodes of severe hypoglycemia and the presence of autoantibodies against endogenous insulin and markedly elevated plasma insulin levels in patients without prior exposure to exogenous insulin [1]. Reports indicate that autoimmune processes are related to the expression of certain major histocompatibility complex (MHC) antigens. Genetic predisposition to IAS is associated with polymorphisms in exon 2 of the HLA-DRB1 gene of the human leukocyte antigen (HLA) class II [2].

A strong association has been described in the Japanese population between IAS and the HLA-DRB1*04:06 alleles, and to a lesser extent with HLA-DRB1*04:03 and HLA-DRB1*04:07, but this association is rare in the Caucasian population [3]. These DNA changes lead to the presence of glutamine at position 74 (shared by all three alleles) and serine at position 37 (exclusive to DRB1*04:06). These amino acids located in essential positions of the protein greatly increase the

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https://doi.org/10.1016/j.crwh.2024.e00644
Received 7 July 2024; Received in revised form 24 July 2024; Accepted 2 August 2024
Available online 10 August 2024

predisposition of an individual to the disease, with the DRB1*04 haplotype being the one with the highest risk [4]. The use of drugs containing sulfhydryl groups by individuals with the aforementioned genetic composition would play a triggering role, as they are capable of reducing the disulfide bonds between the two insulin chains, thus increasing its immunogenicity [5].

The incidence of IAS is difficult to establish due to the rarity of the disease, with most cases described in East Asia [6,7]. To our knowledge, this is the first report of IAS in a Latin American woman with Graves' disease who subsequently became pregnant. We describe follow-up throughout pregnancy, with clinical and molecular evaluation of the patient and her offspring.

2. Case Presentation

A 28-year-old Caucasian woman consulted the endocrinology and diabetes department at a maternity university hospital during her first pregnancy at 8 weeks of gestation. She reported heat intolerance, tremors, and reduced appetite. Six months prior, the patient had received treatment with methimazole (40 mg/day) due to the diagnosis of Graves' disease. Although the initial response to treatment was favorable, after three months she was admitted to the intensive care unit with seizures and depressed level of consciousness secondary to severe hypoglycemia (blood glucose level of 37 mg/dL). She received treatment with lorazepam and intravenous glucose solution. Cerebral computed tomography (CT) was normal, and infectious processes were ruled out. During her hospitalization, she experienced new episodes of severe hypoglycemia that prompted the ruling out of possible causes. Panhypopituitarism and adrenal insufficiency were ruled out as endocrine causes. At this point, blood test results were: C-peptide 19.74 ng/mL (reference: 1.1 to 4.4), insulin 2670 μU/mL (reference: 2.6–24.9), and glucose: 51 mg/dL. These results suggested endogenous hyperinsulinism. A multi-slice helical CT scan of the abdomen was requested, which showed a pancreas with normal morphology. Other causes of hyperinsulinism-induced hypoglycemia such as exogenous insulin or oral antidiabetics use, reactive hypoglycemia, and insulin-producing tumors were ruled out. Hence, based on clinical, biochemical findings, and the fact that anti-insulin antibodies were positive, IAS or Hirata's disease was confirmed. Since this syndrome can be triggered by drugs containing sulfhydryl groups, methimazole was discontinued, and the patient received ablative treatment with 15 mCi of iodine-131 two months before the diagnosis of pregnancy.

Physical examination at 8 weeks of gestation reported a patient weight of 52 kg, height 1.60 m, blood pressure 100/70 mmHg, heart rate 100 beats per min. Ultrasound showed she had a 35 g thyroid gland with decreased consistency and absence of nodules, and bruits were not present upon auscultation. She had mild distal fine tremor in her hands, and her deep tendon reflexes were slightly increased. There were no signs of thyroid ophthalmopathy, with a negative Von Graefe sign. Blood tests at 8 weeks of gestation showed: TSH <0.01 μIU/mL (reference: 0.27–4.2), free T4 1.95 ng/dL (reference: 0.93–1.7), T3 223 ng/dL (reference: 80–200), TSH receptor antibodies (TRab) $>$ 40 IU/L (reference <1.75) blood glucose 86 mg/dL, insulin 6.71 μU/mL, C-peptide 1.25 ng/mL.

Due to the impossibility of re-initiating treatment with methimazole and the difficulty of obtaining propylthiouracil in Argentina as a replacement, surgical treatment of her hyperthyroidism was decided for the second trimester of pregnancy. At 24 weeks of gestation, anti-insulin antibodies, anti-islet cell antibodies, and anti-GAD antibodies were negative. A total thyroidectomy was performed at 25 weeks of gestation, after which there was an optimal postoperative course and maternal-fetal outcome. Subsequently she required temporary supplementation of calcium and calcitriol. Throughout pregnancy fetal monitoring was normal. Ultrasound scan determined a fetal thyroid perimeter of 3.7 cm (50th percentile) at 33 weeks, femoral nucleus ossification consistent with gestational age, and a normal fetal heart. In the same week, under treatment with levothyroxine 100 μg/day, the patient had a normal oral glucose tolerance and TSH 0.18 μIU/mL, free T4 1.07 ng/dL, T3 101 ng/dL, and TRab 22.42 IU/L. At 40 weeks, a healthy female newborn was delivered vaginally (weight 3580 g, length 51 cm, head circumference 33 cm, blood glucose 88 mg/dL, Apgar scores 8/9). The newborn was breastfed and underwent normal neonatal clinical and endocrinological controls. Biochemical blood parameters in relation to time of pregnancy and treatment are presented in Table 1.

After hospital discharge, we decided to investigate the molecular association of IAS with the HLA-DRB1 alleles in the mother and her daughter. Genomic DNA was extracted from peripheral blood leukocytes among both parents and daughter. Sequences were analyzed and compared with the HLA allele library (https://www.ebi.ac.uk/ipd/imgt/hla/alleles/). The following genotypes were identified in the family members: the mother carried HLA-DRB1*03:01/HLA-DRB1*04:01 alleles in compound heterozygosity, the father was identified as homozygous for the HLA-DRB1*08:02 allele, and the daughter as compound heterozygous for HLA-DRB1*04:01/HLA-DRB1*08:02 alleles. Based on these results, genetic counseling was provided to the family, informing about the drugs that both the mother and daughter should avoid. The patient confirmed having no Asian ancestry; however, the HLA-DRB1 genotyping (HLA-DRB1*03:01/HLA-DRB1*04:01) was consistent with Hirata's disease [7].

At 6 months postpartum, the mother was clinically and biochemically euthyroid, under treatment with levothyroxine 150 μg/day, and both her and her daughter's glucose control levels were normal. After 5 years of follow-up, growth, development, and metabolic parameters of the girl were normal.

3. Discussion

IAS is a rare autoimmune condition, especially in Latin America, and most cases are not diagnosed. Other causes of symptomatic hypoglycemia should be excluded when performing differential diagnosis, such as sepsis, diseases of the liver, kidney, or heart, the use of certain drugs, and, less frequently, insulin-secreting tumors (i.e. bronchial carcinoids, gastrointestinal stromal tumors) and tumors producing IGF2, IGF1, somatostatin, and GLP-1 precursors [6]. To confirm the diagnosis of IAS, it is necessary to evidence in the blood the presence of autoantibodies against insulin together with high insulin levels. Additionally, the diagnosis is supported by the association with concomitant autoimmune diseases and the genetic confirmation of carrying HLA alleles associated with Hirata's disease [5,6,8].

In our case, Hirata's disease was suspected because of elevated plasma insulin levels in the presence of a pancreas with normal morphology. The diagnosis was confirmed through the evaluation of autoantibodies against insulin, in addition to the molecular identification of the haplotype associated with autoimmune diseases. As the patient received treatment with methimazole due the diagnosis of hyperthyroidism, it could be assumed that this drug triggered the autoimmune condition causing IAS. On the other hand, it is known that these patients present different autoimmune diseases; in our case, the patient had Graves' disease, which was associated with IAS. The main diagnostic finding was the detection of severe hypoglycemia associated with endogenous hyperinsulinism and elevated C-peptide concentrations. The diagnosis was confirmed by the presence of elevated anti-insulin antibody titers, the absence of pathological abnormalities in the pancreas, and prior exposure to exogenous insulin, as well as the association with genetic polymorphisms in the HLA class II locus (HLA-DRB1 gene, specifically alleles DRB1*04:06, DRB1*04:03, and DRB1*04:07). Although our patient had no Asian ancestry, the HLA typing was consistent with the cases described in the literature for this pathology [8]. Grixti L et al. [9] recently published a review on the genetic aspects of Graves' disease. Around 50% of patients with Graves' disease who have European ancestry present the HLA DRB1*03:01 haplotype, which was present in our patient.

Table 1
Biochemical parameters in relation to the time of pregnancy and treatment.

	TSH	Free T4	T3	TSH receptor antibodies	Glucose	Insulin	C- peptide	Treatment
Reference value	0.27–4.2 μIU/mL	0.93–1.7 ng/dL	80–200 ng/dL	< 1.75 IU/L	70–110 mg/dL	2.6–24.9 μU/mL	1.1–4.4 ng/mL	
Pre-gestational	<0.01	7	300	> 40	51*	2670	19.74	Methimazole ^{131}Iodine
8th week of gestation	<0.01	1.95	223	> 40	86	6.71	1.25	
25th week of gestation	<0.01	1.90	200	> 40	80			Thyroidectomy
33rd week of gestation	0.18	1.07	101	22.42	76			Levothyroxine

* Upon admission glucose was 37 mg/dL.

Once a diagnosis of IAS is made, it is important to identify the trigger to avoid new or greater exposure. In this case, most likely the sulfhydryl group of the methimazole molecule was the activating agent, since anti-insulin antibodies became negative upon discontinuation of the drug with normalization of blood glucose levels [5], despite the fact that Graves' disease was still active.

Overt hyperthyroidism is present in around 0.1–0.4% of pregnant women, diagnosed by a reduced serum TSH with high free T4 and/or free T3 levels, using trimester- and laboratory-specific reference ranges. Autoimmune Graves' disease is the most common cause of hyperthyroidism. Uncontrolled Graves' thyrotoxicosis has been associated to adverse maternal-fetal outcomes, such as miscarriage, preeclampsia, preterm birth, placental abruption, and fetal hyperthyroidism. Fetal hyperthyroidism should be suspected when there are elevated TRab levels (usually >3–5 times) starting from the 20th week of gestation in mothers with active or in remission hyperthyroidism. In addition to TRab, a sustained fetal heart rate above 160 beats per minute, as well as fetal ultrasonographic parameters (i.e. goiter, accelerated bone maturation, or heart failure) support the diagnosis of fetal hyperthyroidism. Although our patient had elevated TRab, which can cross the placental barrier and affect fetal health, these antibodies have a positive predictive value of 40–50%, which is why some pregnant women with very high TRAa levels do not have children with hyperthyroidism. Ultrasonographic follow-up by fetal medicine specialists allows, as in our case, the monitoring of pregnancy progression in order to rule out fetal involvement [10,11].

During the first half of pregnancy, normal glucose ranges can be considered hypoglycemic if compared with non-pregnant women, representing a physiological adaptation of pregnancy. However, this phenomenon could be misleading in our case, because IAS disappears 3 to 6 months after discontinuing the responsible agent.

We could find in the literature only one case of a 28-year-old pregnant Chinese woman with a history of Graves' disease treated with methimazole, who presented severe hypoglycemia and hyperinsulinemia episodes at 10 weeks of gestation. The patient lost her pregnancy, methimazole was discontinued, and she was treated with propylthiouracil and prednisone with a good response [12]. The obstetric follow-up of our patient was multidisciplinary and required serial blood biochemical and ultrasound controls to evaluate maternal-fetal health. In our case, despite the fact that, prior to pregnancy, when IAS was diagnosed, methimazole had already been discontinued and then treated with radioactive iodine, at the time of pregnancy antibodies were negative. We still doubt whether pregnancy itself could mask new hypoglycemia episodes in a genetically predisposed person in the context of an active autoimmune disease. The option of surgical treatment was taken because propylthiouracil is not marketed in Argentina, and it is among the drugs that can trigger IAS [1].

To our knowledge, this is the first published case of IAS in a Latin American woman with Graves' disease who subsequently becomes pregnant. In addition, molecular genotyping was performed suggesting that these HLA DR4 alleles could be associated with IAS in our region in the absence of an Asian ancestry. High-resolution DNA-based techniques indicate that HLA DRB1*03 is the main risk factor for type 1 autoimmune hepatitis among Caucasian adults in Northern Europe, and HLA DRB1*04 is an independent secondary risk factor in the same population [13]. Patients with DRB1*04:01 may have less T-cell activation and present with less severe disease than patients with DRB1*03:01 due to sequence differences. In contrast, individuals with DRB1*04:01 have a greater number of different proteins expressed on the surface of antigen-presenting cells than those with DRB1*03:01, and therefore may have a greater ability to develop responses to non-hepatic autoantigens and a greater likelihood of developing autoimmune reactions affecting other organs [7,8]. The greater the number of HLA alleles encoding the critical amino acid on the cell surface, the greater is the likelihood of disease. In this model, individuals homozygous for a given haplotype have a higher risk of severe disease [8,12].

Disease susceptibility determinants may be shared by several diseases, and shared susceptibility can promote the clustering of HLA-associated diseases in families and patients, reflecting an autoimmune tendency [13]. The ancestral haplotype 8.1 includes additional risk factors for autoimmunity, particularly TNFα*2 and C4B*Q0, as well as DRB1*03:01, and these may non-selectively amplify autoimmune reactions leading to more severe disease and also increase the likelihood of concurrent immune diseases occurring in the same individual [4].

Hirata's disease tends to present spontaneous remission in 80% of cases three to six months after the withdrawal of the triggering agent. Current treatment is based on discontinuing the triggering drug, a fractional diet, and corticosteroid therapy, due to its potential benefit in reducing the frequency and severity of hypoglycemia, as well as anti-insulin autoantibodies [1].

In conclusion, a thorough medical history, exploring the background of autoimmune disease, as well as the use of drugs with a sulfhydryl group, should aid the clinical suspicion of IAS related hypoglycemia. Although HLA analysis cannot be performed in all patients, it would be important to evaluate the genetic predisposition in the offspring in order to promptly provide adequate counseling.

Contributors

Carolina Fux-Otta contributed to patient care, conception of the case report, acquiring and interpreting the data, undertaking the literature review and critically revising the article for important intellectual content.

Raúl Reynoso contributed to the execution and interpretation of the molecular studies.

Peter Chedraui contributed critically revising the article for important intellectual content.

Paula Estario contributed to the initial diagnosis of the pathology, collaborated in the interpretation, and assisted in the writing of the manuscript.

María E. Estario contributed to the initial diagnosis of the pathology, collaborated in the interpretation, and assisted in the writing of the

manuscript.

Gabriel Iraci contributed to the interpretation of molecular studies, the drafting of the manuscript, and its critical review.

Noelia Ramos contributed to the care and follow-up of the patient as well as the newborn.

Mariana Di Carlo contributed to the care and follow-up of the patient as well as the newborn.

Victoria Gamba contributed to the care and follow-up of the patient as well as the newborn.

Adela Sembaj contributed to the execution and interpretation of the molecular studies.

All authors approved the final submitted manuscript.

Funding

No funding from an external source supported the publication of this case report.

Patient consent

Patient consent was obtained for the publication of this case report.

Provenance and peer review

This article was not commissioned. Peer review was directed by Professor Margaret Rees independently of Peter Chedraui and Carolina Fux Otta, an editor and editorial board member respectively of *Case Reports in Women's Health*, who were blinded to the process.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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