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LETTER TO THE EDITOR

RECURRENT DRUG-INDUCED INSULIN AUTOIMMUNE SYNDROME IN A PATIENT WITH PREMATURE OVARIAN FAILURE

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Insulin autoimmune syndrome (IAS) is characterized by hypoglycemic attacks, very high insulin levels and the presence of circulating autoantibodies to insulin in patients who have not been treated with exogenous insulin. Approximately half of patients with insulin autoimmune syndrome have a medication history preceding hypoglycemic events. We present the case of a young woman with premature ovarian failure who developed IAS initially after treatment with methimazole and several years later after captopril, and because of coexistent premature ovarian failure was classified as having autoimmune polyglandular syndrome (APS) type 3. Termination of methimazole and captopril treatment resulted in the disappearance of hypoglycemic episodes. We discuss diagnostic and treatment dilemmas associated with discovering and management of IAS and APS in this patient.

Insulin autoimmune syndrome (IAS), or Hirata disease, is characterized by the combination of fasting hypoglycemia, high concentrations of total immunoreactive insulin, and the presence of autoantibodies to native human insulin in serum (1-3). Although in Japanese patients, IAS is the third leading cause of spontaneous hypoglycemic attacks, in the remaining countries it is regarded as a very rare cause of hypoglycemia (2). Approximately half of IAS patients have a medication history preceding hypoglycemic events, and over 90% of the agents are sulfhydryl compounds such as methimazole, N-2 mercaptopropionylglycine, or glutathione (4). As described in our article, in genetically predisposed patients, IAS may constitute a component of autoimmune polyglandular syndromes (APS).

Patient's presentation

The first health problems in a now 39-year-old Caucasian (Polish) female occurred at the age of 26, when the patient developed secondary amenorrhea. She was an overweight (BMI - 27.8 kg/m^2) non-smoker with a family history of autoimmune disorders (her mother and sister both suffered from lymphocytic thyroiditis) but not of hypertension. Suggestive clinical symptoms (hot flashes, vaginal dryness and dyspareunia) combined with markedly elevated gonadotropin levels (FSH – 140 U/L, LH – 32 U/L), low estradiol levels (26 pmol/L) and a greatly diminished follicle count, as seen on transvaginal ultrasonography of the ovaries, indicated the presence of premature ovarian failure (POF). The patient was prescribed with estrogen replacement therapy, which was continued throughout the observation period. At the age of 30, she was diagnosed with overt hyperthyroidism (TSH – 0.002mIU/L, reference values: 0.45-4.5mIU/L; free thyroxine – 2.34ng/mL, reference values: 0.90-1.7ng/dL; free

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triiodothyronine – 7.22pg/mL, reference values: 2.77-5.27pg/mL) secondary to Graves' disease (thyrotropin receptor antibodies – 10.7U/L, reference values <1.0U/L) and started methimazole treatment (30 mg daily). Four weeks later she developed recurring hypoglycemia symptoms. Each time these symptoms were observed during the postprandial state and were relieved by ingestion of the meal. The last episode was severe (plasma glucose – 28mg/dL) and subsided only after intravenous infusion of glucose solution, but reappeared soon thereafter. Although the clinical picture and markedly increased circulating levels of insulin, C-peptide and proinsulin suggested insulinoma (Table I), the presence of insulin antibodies in a high titer as well as normal findings on abdominal nuclear magnetic resonance and celiac angiography made it possible to diagnose IAS. Because the appearance of IAS was attributed to methimazole treatment, methimazole was replaced with propylthiouracil and 2 months later the patient underwent radioiodine ablation. Cessation of methimazole treatment resulted in a spontaneous normalization of plasma glucose levels and no hypoglycemic events occurred for the following 5 years. At the age of 35, because of stage 1 arterial hypertension the patient was recommended by a general practitioner to use captopril at the daily dose of 75 mg. After 2 weeks of treatment, she was admitted to our clinic because of hypoglycemic coma associated with extremely low plasma glucose levels (15 mg/dL). The presence of insulinoma was again excluded (Table I). Although the patient was seropositive for 21-hydroxylase and 17α-hydroxylase antibodies, normal morning plasma ACTH levels, morning plasma cortisol and a peak cortisol level in a 250 μg cosyntropin stimulation test as well as plasma renin activity and aldosterone levels within the reference range ruled out the presence of adrenal insufficiency. HLA typing showed that the patient was DRB1 *0406 positive. No autoimmune regulator (AIRE) gene mutation was detected but she was found to have antibodies against liver and kidney microsomes (anti-LKM). Because hypoglycemia was attributed to captopril treatment, this therapy was immediately withdrawn (captopril was replaced with lacidipine), which resulted in the disappearance of hypoglycemia. Since that time to date the patient has not experienced any hypoglycemic episodes.

Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION

In our patient, IAS manifested for the first time at the age of 30 and was induced by methimazole treatment. This finding is in line with observations by Uchigata at al. (5) indicating that, unlike other cases of IAS, methimazole- and carbomazole-induced IAS in patients with Graves' disease often develops in young females between the ages of 10 and 29. Interestingly, our patient experienced hypoglycemic symptoms not in a fasting state but several hours after the last meal. This finding, observed in most patients with IAS, may be attributed to the increase in insulin activity due to the dissociation of insulin from its antibodies, which cannot be counterbalanced by further absorption of glucose (6).

Another interesting observation was that our subject developed IAS after treatment with two different drugs. The association between therapy and this disorder is not accidental because each time the symptoms disappeared shortly after drug withdrawal. Although methimazole treatment is considered the most common cause of drug-induced IAS while captopril was also found to induce this syndrome previously (2), our patient is the first one in whom IAS was caused by more than one agent. Taking into account the large number of patients treated with methimazole and captopril, and only few cases of iatrogenic IAS, we may assume that both drugs carry the risk of inducing IAS only in selected groups of patients demonstrating a susceptible genetic background for autoimmune diseases. This situation took place in our patient who was a carrier of DRB1 *0406 allele, associated with the increased risk of IAS (7, 8). Interestingly, both methimazole (9) and capropril (10) had a sulfhydryl group in their structure and may either cleave disulfide bonds in the insulin molecule, or due to the presence of this group, they may enhance immune responses resulting in the development of IAS (2).

Although many patients with IAS were diagnosed with Graves' disease, the concomitant presence of this syndrome and other autoimmune disorders have been reported only in two cases: in a 22-year-old woman suffering from coexisting lupus erythematosus (11),

Table I. *Hormonal characteristics of the patient.*

Hormone (Unit)	Reference values	First hospitalization[1]	After methimazole withdrawal	Second hospitalization[2]	After captopril withdrawal
Insulin (mU/L)	6.0-25.0	2 255	12.3	2 832	8.5
C-peptide (μg/L)	0.6-2.0	10.5	0.8	12.1	0.9
Proinsulin (pmol/L)	4.2-12.4	30.3	7.4	39.2	8.3
Insulin autoantibodies (U/L)	<1.0	82.5	0.8	107.8	0.6
Glutamic acid decarboxylase antibodies (ng/mL)	<32	12	Not investigated	8	Not investigated
IA2 antibodies[3]		Negative	Not investigated	Negative	Not investigated
FSH (IU/L)	3.4-12.5	93.2	89.1	86.7	82.2
LH (IU/L)	2.3-12.7	35.2	40.2	32.4	30.8
ACTH (ng/L)	20.0-60.0	24.5	28.7	30.4	23.8
Morning plasma cortisol (μg/dL)	>7.0	12.3	11.5	10.3	11.6
Plasma cortisol *in the 250-μg cosyntropin test* (μg/dL)	>19.6	25.1	Not investigated	22.3	Not investigated
Urine free cortisol (μg/day)	20-90	68	Not investigated	72	Not investigated
Plasma renin activity[4] (ng/mL/hr)	0.3-2.8	1.6	Not investigated	1.7	Not investigated
Aldosterone[4] (pg/mL)	30-150	68	Not investigated	78	Not investigated
DHEA-S (μg/dL)	80.0-450.0	380	Not investigated	358	Not investigated
21-hydroxylase antibodies		Positive	Positive	Positive	Positive
17α-hydroxylase antibodies		Positive	Positive	Positive	Positive
TSH (mIU/L)	0.4-4.5	1.83	1.47	1.72	1.86
Free thyroxine (pmol/L)	12.0-22.0	14.2	18.7	17.9	17.1
Free triiodothyronine (pmol/L)	2.8-6.0	3.5	4.1	4.0	3.8
Thyroid peroxidase antibodies (U/mL)	<100	22	27	18	20
Thyrotropin receptor antibodies (U/L)	<1.0	0.4	Not investigated	0.3	Not investigated

[1]*because of methimazole-induced hypoglycemia*
[2]*because of captopril-induced hypoglycemia*
[3]*Protein tyrosine phosphatase-like protein IA2-antibodies*
[4]*In the supine position*

and in a 75-year-old man with slowly progressive type 1 diabetes (12). Both patients were effectively treated with high doses of steroids (plus cyclophosphamide in the first case). This report is the first one describing a coexistence of IAS and premature ovarian failure (POF). Taking into account the autoimmune nature of both IAS (1-3) and POF (13), the occurrence of Graves disease in the past as well as the presence of 21-hydroxylase and 17α-hydroxylase antibodies and positive anti-LKM antibodies, we could diagnose our patient as having APS. These syndromes are conditions characterised by the association of 2 or more organ-specific disorders (14, 15) which, on the basis of the clinical picture according to the classification proposed by Neufeld and Blizzard (16), may be divided into 4 different types. Because the patient had suffered in the past from Graves' disease and throughout the entire observation period did not develop mucocutaneous candidiasis, hypoparathyroidism and Addison's disease, as well as because she did not have any AIRE gene mutation, she was diagnosed with APS type 3. Although over 8 years have passed since our patient was diagnosed with APS, the probability of the development of adrenal insufficiency in this woman, positive for 21-hydroxylase and 17α-hydroxylase antibodies, is however still high. Because most patients having both these antibodies develop Addison's disease, it is likely that in the future she will be reclassified as type 2.

Like most Asian patients with IAS, our patient was positive for DRB1*0406. Although it cannot be completely excluded that IAS simply coincided with POF, this situation seems rather unlikely. Before the age of 30, POF affects only 0.1% of women, (13-17) while in the Caucasian population, to date, IAS has been described in less than 50 patients (2). Moreover, our patient had other autoimmunities as well as a family history of autoimmune disorders, which strongly suggest the autoimmune nature of her health problems. It should be remembered that, compared to type 1, genetic susceptibility for APS type 2 and particularly type 3 is less understood (14, 15).

To sum up, all patients diagnosed with any autoimmune disorder who develop hypoglycemia symptoms should be assessed for the presence of IAS. Patients with IAS induced by one drug containing a sulfhydryl group should not be treated with other agents having this group in their structure.

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