Hirata's Disease: Rare Cause of Hypoglycaemia in Caucasian Male

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ABSTRACT
Insulin autoimmune syndrome or Hirata's disease is an extremely rare condition leading to hypoglycaemia of variable severity due to autoantibodies against insulin. We present the first case documented in the Czech Republic.

KEYWORDS
hyperinsulinemic hypoglycaemia; insulin autoantibodies; Hirata's disease; insulin autoimmune syndrome

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BACKGROUND

Insulin autoimmune syndrome or Hirata's disease is a rare disorder manifested by episodes of hypoglycaemia in the patient without previous treatment by insulin or its analogues. This condition is the third most prevalent cause of hyperinsulinemic hypoglycaemia in Asians, whereas it is extremely rare in the Caucasian population. Insulin autoimmune syndrome (IAS) is an infrequent condition characterised by episodes of postprandial and/or fasting hypoglycaemia and the presence of autoantibodies against endogenous insulin in patients with no prior exposure to exogenous insulin (1). It's named after Y. Hirata, who described this disease for the first time in 1970 (2). It affects mainly adults between 40–60 years of age with no difference in sexes, although some cases in children were also described (3–5). The exact prevalence is difficult to assume because of the rarity of the disease. The most cases were described in Eastern Asia, especially in Japan, where it is considered to be the third leading cause of hyperinsulinaemic hypoglycaemia right after insulinoma and extrapancreatic neoplasias (6). This condition seems to be significantly less frequent in other countries. However, the number of cases is generally rising in the last decade, probably due to higher awareness of the disease. In this paper, we would like to present, to our knowledge, the first case of IAS documented in the Czech Republic to spread awareness across the clinicians and to prevent a misdiagnosis of this rare condition.

CASE PRESENTATION

A 40-year-old Caucasian male was referred to our department with episodes of dizziness, hunger, sweating and blurry vision lasting ten days. These symptoms usually occurred 2–3 hours after the meal and during the night and got more severe and frequent in the past few days. He claimed there was a significant relieve after food administration. Before the admission to our department, the lowest measured glycaemia value was 2.6 mmol/l (normal range 3.9–5.6 mmol/l) and considerable elevation of C-peptide (6620 pmol/l, normal range 260–1730 pmol/l) was found. However, no abnormality on abdominal ultrasound was found; he was referred to our clinic with a high suspicion for insulinoma for further diagnostic evaluation.

His past medical history was significant for pollinosis, gastroesophageal reflux disease and low back pain. He used antihistaminics (levocetirizine) and topic corticosteroid (fluticasone) occasionally during the pollen season. He confessed taking Revitanerv (OTC preparation containing vitamins and alpha-lipoic acid) for leg and back pain for one month with the last administration eighteen days before the admission. There was no autoimmune or endocrine disease in family history, besides the fact that his father died of pancreatic cancer. He denied smoking and drinking alcohol or any drug abuse. His vital functions and physical examination at the admission were completely normal, except for being overweight with a BMI 27.7 kg/m^2 (80 kg/170 cm). Blood count was normal. Biochemistry revealed a slight elevation of liver enzymes and hyperuricaemia.

INVESTIGATION

Because of symptomatic hypoglycaemia (3.3 mmol/l) at admission and insufficient peroral food intake due to nausea we started an intravenous 10% glucose infusion to maintain the serum glucose level within the physiologic range. We performed the fasting test. Our patient developed symptomatic hypoglycaemia 2.3 mmol/L in 160 min with serum Insulin level 31910 mU/l (normal range 2.5–24 mU/l) and C-peptide 6304 pmol/l (normal range 260–1730 pmol/l). These findings did not support the diagnosis of an insulinoma, neither did imaging studies – CT of the abdomen showed only small stone in the gallbladder. Incipient chronic pancreatitis with no focal lesion was visible on endoscopic ultrasound examination.

We considered the possibility of an autoimmune form of hypoglycaemia in the differential diagnosis because of the inadequate elevation of serum level of Insulin, C-peptide and the insulin to C-peptide molar ratio equal to 5 (normal ratio < 1). The presence of autoantibodies against the endogenous insulin was confirmed by precipitation in 25% PEG – result of insulin after the process was 326.2 mU/l which is equal to 1,26% (compared with insulin level before the precipitation – 25860 mU/l). The same test with C-peptid showed the result of 17% (level before – 6204 pmol/l, after – 1056 pmol/l). ELISA was performed (Commercial kit Anti-Insulin, DIALAB Produktion und Vertrieb von chemisch-technischen Produkten und Laborinstrumenten Gesellschaft m.b.H., Austria) to determine the exact level of autoantibodies against human insulin, with the result of IAA 395.4 U/ml (reference range 0–10 U/ml). Further laboratory studies showed no abnormalities in serum cortisol level, CGA, thyroid gland function, serum protein electrophoresis and screening for rheumatologic autoantibodies (Table 1). Since the signs of possible type B insulin resistance (acanthosis nigricans, hyperandrogenism, hyperglycaemia and elevated HbA1c) were absent, we did not evaluate insulin receptor autoantibodies.

TREATMENT AND FOLLOW-UP

Peroral corticosteroids in a high dosage were started (Prednisone 1 mg/kg per day) and dietary modification with the elimination of high glycaemic index carbohydrates was implemented. Because of the persistent severe hypoglycaemia every night, therapeutic plasmapheresis was performed four times in total within the hospitalisation. After 43 days in total, with a significant decrease of serum insulin serum (1020.1 mU/l) and IAA titters (1.9 U/ml), our patient was discharged with a home medication of Prednisone 0.5 mg/kg per day.

Corticosteroids were slowly tapered down during regular follow-up. Nevertheless, the IAA titters gradually increased, and episodes of symptomatic hypoglycaemia occurred again. As a side effect of the long-lasting corticosteroids therapy, a deep vein thrombosis was diagnosed and treated. Another plasmapheresis was performed to

Tab. 1 Laboratory findings at the time of diagnosis, February 2020.

Analyte	Patient's value	Reference range
Sodium (mmol/l)	142	136–145
Potassium (mmol/l)	4.2	3.5–5.1
Chloride (mmol/l)	106	98–107
Urea (mmol/l)	2.2	2.8–8.1
Creatinine (umol/l)	77	45–84
Uric acid (umol/l)	427	143–339
Alcalic phosphatase (ukat/l)	1.35	0.58–1.75
Aspartate aminotransferase (ukat/l)	1.52	0.17–0.6
Alanine aminotransferase (ukat/l)	2.54	0.17–0.58
Gamma-glutamyl transferase (ukat/l)	0.82	0–0.67
Bilirubin (umol/l)	3	0–15
C-reactive protein (mg/l)	0.6	0–5
Total protein (g/l)	71	64–83
Albumin (g/l)	44.8	35–52
Glucose (mmol/l)	3.3	3.9–5.6
Insulin (mU/l)	31910	2.5–24
C-peptide (pmol/l)	6304	260–1730
HbA1c (mmol/mol)	38	20–42
TSH (mU/l)	1.6	0.27–4.2
fT4 (pmol/l)	14.6	12 – 22
TRAK (kU/l)	1.1	0–1.8
ATPO (kU/l)	29.3	0–34
ATG (kU/l)	12.7	0–115
Chromogranine A (ug/l)	53.19	0–101.9
Rheumatoid factor (latex fixation)	negative	
ANA immunofluorescence	negative	
ANCA immunofluorescence	negative	
ENA screening profil	negative	
anti-dsDNA	negative	
Anti-CCP (U/ml)	0.10	0–25
anti-insulin antibodies (U/ml)	337	0–10
Cortisol (nmol/l)	258	138–690
Red blood count (× 106)	5.17	4–5.8
Hemoglobin (g/l)	153	135–175
White blood count (× 109/l)	7.8	4–10
Platelet count (× 103/l)	204	150–400
PT (ratio)	0.82	0.8–1.2
APTT (ratio)	0.84	0.8–1.2

TSH – thyroid stimulating hormon, fT4 – free thyroxin, TRAK – anti-TSH receptor antibodies, ATPO – anti-thyreoperoxidase antibodies, ATG – anti-thyreoglobulin antibodies, ANA – anti-nuclear antibodies, ANCA – anti-neutrophil cytoplasm antibodies, ENA – extractable nuclear antigen antibodies, anti-dsDNA – anti-double stranded DNA antibodies, anti-CCP – anti-cyclic citrullinated peptid antibodies, PT – protrombin time, APTT – activated parcial tromboplastin time

Tab. 2

Drugs	Infection
Methimazole	Mumps
Propylthiouracil	Rubella
Carbimazole	Coxsackie B influenza
Alpha-lipoic acid	Hepatitis C
Prytinol	Varicella zoster virus
Glutathione	Measles
Methionine	
α-mercaptopropionil glycine	
Captopril	
Hydralazine	**Other conditions**
Torasemide	MGUS
Diltiazem	Multiple myeloma
Procainamide	Rheumatoid arthritis
Loxoprofen-sodium	SLE
Steroids	
Penicillamine	
Penicilin G	
Imipenem	
Isoniazid	
Alpha-interferon	
Acegratone	
Pantoprazole	
Clopidrogrel	
Albumin	
Gliclazide	
Garlic	

Assumed and revised by Censi et al. Ann Transl Med 2018; Sep; 6(17): 335.
MGUS – monoclonal gammopathy of undetermined significance,
SLE – systemic lupus erythematodes

reduce IAA level, and then immunotherapy with Rituximab (anti CD20 chimeric monoclonal antibody) in two doses of 1 g was applied with a significant decrease of IAA and complete elimination of symptomatic hypoglycaemic episodes. At follow up six months after diagnosis, our patient remained asymptomatic on Prednisone 0.25 mg/kg per day only (Figure 1).

DISCUSSION

We present the first case of IAS described in the Czech Republic. Etiopathological background of IAS is based on the presence of a combination of genetic predisposition and exogenous trigger. Mechanism of onset has been classified as a type VII hypersensitivity – a presence of autoantibodies against molecules circulating in the blood (7). This condition was associated more frequently with particular alleles of HLA antigens – specifically with HLA DRB1*0406 and less frequently with DRB1*0403(8). The

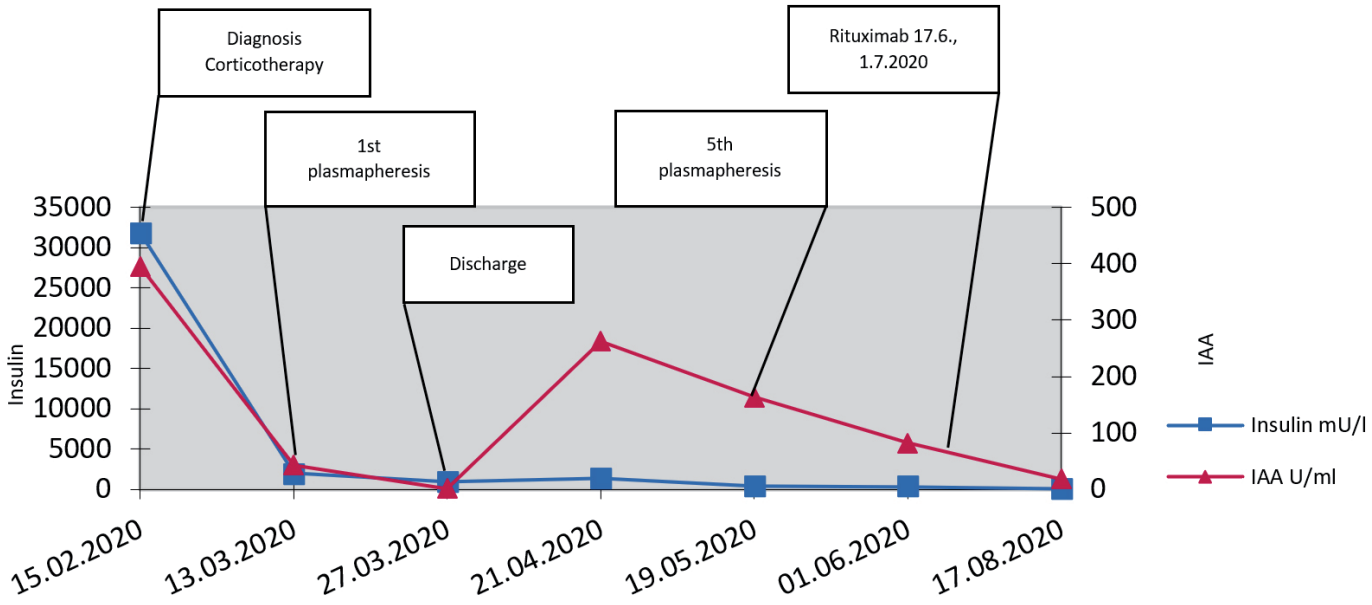

Fig. 1 Serum levels of insulin and anti-insulin autoantibodies during the treatment and follow-up.

first mentioned has a high prevalence in the Asian population, especially in Japan, which may explain a geographic distribution of IAS. The second cause taking part in the process of induction of the immune system starting the production of autoantibodies can be a viral infection or the exposition to drugs – especially the ones containing a sulfhydryl compound (Table 2) (9). Drug-induced onset was also present in our case. In our patient, the trigger was revealed later, after careful history taking. The patient has admitted administration of preparation containing alpha-lipoic acid. Drug-induced etiology is documented in more than 50% IAS cases. The presumed mechanism of development is deemed to be an interaction between the reductive part of the drug and the disulphide bonds in the insulin molecule which makes its structure more immunogenic due to molecular mimicry phenomenon (1, 10). Association between administration of alpha-lipoic acid, often used for a peripheral polyneuropathy, was firstly published in 2006 by Furukawa (11). Since then, others reported cases in both Asian and Caucasian population as the frequency of its use is rising (12–14). Besides the drugs and infection trigger, IAS was also documented together with another autoimmune inflammatory disease such as rheumatologic (rheumatoid arthritis, systemic lupus erythematodes), endocrine (Graves' disease) (1, 5) and also with the hematologic disease (monoclonal gammopathy of undetermined significance, multiple myeloma) (3). Spontaneous onset was also described in minor cases (3).

Refractory of the disease is also unique in our case. IAS is mostly a self-limited disorder, in some cases treated even with dietary modification and corticosteroids. In our case, several plasmapheresis and immunotherapy with Rituximab had to be applied to maintain blood glucose at a normal level. The therapeutic approach varies from the discontinuation of certain drug and diet modification to aggressive immunosuppressive therapy in cases with persistent severe hypoglycaemia. In most patients (over 80%) disease spontaneously resolved after drug withdrawal or with a restriction of high glycaemic carbohydrates food intake and increased frequency of meals (16). High dose corticosteroids are commonly used. Alpha-glucosidase inhibitors can also be used to lower postprandial blood glucose level as a stimulus for further secretion of insulin, but its intake is accompanied by frequent gastrointestinal discomfort. Nevertheless, in the minority of cases refractory to corticosteroids and regimen adjustment, it requires aggressive immunosuppressive therapy, as in our case. In the literature, the application of Cyclophosphamide, cyclosporin A, mycophenolate mofetil (3), azathioprine (16) and Rituximab (17) was documented, however, no randomised clinical trial was performed, or clinical effect of each regimen was analysed, so far to our best knowledge. Plasmapheresis also can be performed with the aim of faster decreasing serum IAA levels (17). In contrast with most other cases of ALA induced IAS the disease was not self-limiting, our patient required aggressive therapeutic approach – a combination of corticosteroids, plasmapheresis, and Rituximab with a significant clinical and laboratory effect. Pathogenesis of the IAS consists of interaction between the IAA and insulin and/or in the same cases proinsulin molecules by creating a macromolecule hindering its biologic effect. During a postprandial hyperglycaemic episode, insulin is secreted in pancreatic beta-cells to maintain blood glucose level within normal range and ensure proper glucose metabolism. When the significant titter of IAA with accurate affinity and avidity is present, insulin is bound to a macromolecule complex. Further secretion is then stimulated to exceed the capacity of antibodies. Blood glucose level slowly decreases, and insulin is slowly released due to the dissociation of immunocomplexes. Attributes of IAA are documented to be responsible for the duration and severity of hypoglycaemia. Association and dissociation rate constant, antibodies capacity and serum concentration are the most important characteristics, a high binding capacity and low

binding affinity for insulin allow the release of insulin and development of a hypoglycaemia (1, 10). Symptoms usually occur 30–120 days after the initiation of therapy with a certain drug (12) and present themselves as a Whipple's triad – symptomatic and by the laboratory test confirmed hypoglycaemia (blood glucose level < 4 mmol/L) with relief after glucose administration.

Pathognomonic laboratory findings are elevation of serum Insulin (> 24 mU/l, usually over 100–1000 mU/l, a much higher concentration than in insulinoma), elevated or normal serum C-peptide (260–1730 pmol/l) and detection of IAA (3). Insulin to C-peptide molar ratio can also be used. Usually, it should be less than one, whereas, in patients with IAS, it is usually > 1 (3). This diagnostic tool is not specific enough in view of a possibility of the presence of autoantibodies against both insulin and C-peptide in the same patient. In case of production of C-peptide binding autoantibodies the ratio can be false normal because of prolonged t1/2 due to its binding to IAA (10). Macrocomplexes of IAA and insulin can be assessed by precipitation in polyethene-glycol (15). Exact titter is later determined by ELISA (10). Administration of exogenous insulin or other hypoglycaemic medication, e.g. sulphonylurea should be considered in the differential diagnosis. In our patient symptoms typically started four weeks after administration of a preparation, presenting both adrenergic and neuroglycopenic symptoms 2–6 hours after the meal.

An extreme elevation of serum insulin and no abnormality on imaging studies brought us to a diagnosis of IAS, the first published case in the Czech Republic.

CONCLUSION

IAS should be considered a possible diagnosis in all cases of hyperinsulinaemic hypoglycaemia in non-acutely ill patients to prevent unnecessary expensive imaging studies and potentially harmful surgical procedures. In cases refractory to dietary regimen and corticosteroids, or cases when corticosteroids have considerable side effects, Rituximab and plasmapheresis should be considered as an alternative treatment.

PATIENTS CONSENT

Informed consent has been obtained from the patient.

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