Endocrinology, Diabetes & Metabolism CASE REPORTS

M Yukina and others | Insulin autoimmune syndrome

ID: 19-0159; June 2020
DOI: 10.1530/EDM-19-0159

Insulin autoimmune syndrome

Marina Yukina[1], Nurana Nuralieva[1], Maksim Solovyev[1], Ekaterina Troshina[1,2] and Evgeny Vasilyev[3]

[1]Department of Therapeutic Endocrinology, Endocrinology Research Centre (ERC), Moscow, Russia, [2]Russian Academy of Sciences, Endocrinology Service, Department of Therapeutic Endocrinology, Endocrinology Research Centre (ERC), Moscow, Russia, and [3]Laboratory of Inherited Endocrine Disorders, Endocrinology Research Centre (ERC), Moscow, Russia

Correspondence should be addressed to M Solovyev
Email
maxsolovej@mail.ru

Summary

Insulin autoimmune syndrome (Hirata's disease) is a disorder caused by development of autoantibodies to insulin and manifested by hypoglycaemic syndrome. The overwhelming majority of physicians do not include it in the differential diagnosis of hypoglycaemic states because of a misconception of an extremely low prevalence of this condition. This results in unnecessary drug therapy and unjustified surgical interventions in patients that otherwise would be successfully treated conservatively. This disease is strongly associated with certain alleles of the HLA gene. In most cases, this condition develops in predisposed individuals taking drugs containing sulfhydryl groups. Formation of autoantibodies to insulin may be observed in patients with other autoimmune disorders, as well as in those with multiple myeloma or monoclonal gammopathy of undetermined significance. This paper presents the first Russian case report of insulin autoimmune syndrome in an adult patient.

Learning points:

- Insulin autoimmune syndrome, Hirata's disease, anti-insulin antibodies, and hypoglycaemia.

Background

Insulin autoimmune syndrome (IAS, Hirata's disease) is one of the causes of hypoglycaemic syndrome and is due to formation of autoantibodies to immunoreactive insulin (IRI-Ab). Hypoglycaemic syndrome is a complex of symptoms associated with decreased blood glucose levels (hypoglycaemia) and neuroglycopenic symptoms and relieved by the administration of glucose. Severe hypoglycaemia is a life-threatening condition due to high risk of hypoglycaemic coma and a fatal outcome.

Formation of IRI-Ab may be observed in patients with other autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus (SLE), or polymyositis (1, 2)), multiple myeloma, or monoclonal gammopathy. Furthermore, there have been cases where hypoglycaemic syndrome was the first manifestation of a haematological disease.

Autoimmune processes have been shown to be related to certain antigens of major histocompatibility complex (MHC). IAS is known to be strongly associated with allele DRB1*04:06 and, to a lesser extent, with alleles DRB1*04:03 and DRB1*04:07. This association is believed to be attributable to essential glutamine at position 74 (shared by all three alleles) and serine at position 37 (unique to DRB1*04:06) greatly increases an individual's predisposition to the disease (3). All the aforementioned variants belong to the increased-risk haplotype DRB1*04, DQA1*03:01, and DQB1*03:02.

Most IAS cases have been described in Japan (380 patients (4)) (5) and in other East Asian countries (including 142 cases in China (6)), which can probably be explained by the high frequency of the DRB1*04:06 allele in these populations. In Europe and America, the incidence of the disease is lower (70 patients with IAS have been reported (7)), as the DRB1*04:06 allele is extremely rarely observed and predisposition is mainly linked to

Table 1 Medicinal products inducing IAS.

Medicinal product	Percentage of the product-induced cases in the total number of IAS cases in China
Methimazole	64.5
Insulin	11.2
Tiopronin	6.4
Propylthiouracil	4.8
Penicillamine	2.4
Alpha-lipoic acid	1.6
Amlodipine	1.6
Captopril	1.6
Carbimazole	0.8
Propranolol	0.8
Anti-tuberculosis drugs	0.8
Pyritinol	0.8
^{131}I	0.8

Adapted from Zeng *et al*. (6).

DRB1*04:03 (8). No cases of IAS in adult patients have been described in Russia, most probably due to the fact that most physicians do not include IAS in the differential diagnosis of hypoglycaemia. Besides, mild cases of this disease often remain undiagnosed. It is thus assumed that the prevalence of this condition is significantly higher.

In over 50% of all cases, the development of IAS is preceded by use of drugs containing sulfhydryl groups (6) (Table 1). IAS usually develops a few weeks after the start of drug therapy: IRI-Ab begin to form during this period as a result of increased immunogenicity of the hormone due to a change in its molecular structure, which results from breakage of the disulfide bonds of insulin by the sulfhydryl groups of the drug substance (9).

Hypoglycaemia associated with IAS usually develops 3–4 h after meals, following an early postprandial hyperglycaemia. The increasing glucose level is most probably due to rapid binding of insulin by the antibodies during the postprandial phase, which leads to decreased biological activity of the hormone. This, in turn, results in prolongation of insulin secretion. The forming complex dissociates 3–5 h after the meal, releasing a considerable amount of insulin that causes hypoglycaemia (9). Laboratory tests performed at the peak hypoglycaemia reveal extremely high levels of insulin, C-peptide, and proinsulin (10, 11).

Most attacks of hypoglycaemia in patients with IAS are transient and resolve spontaneously 3–6 months after diagnosis, particularly quickly after discontinuation of the culprit drug. Insulin and IRI-Ab levels gradually decrease. Besides, frequent meals with a low content of complex carbohydrates and containing no simple carbohydrates (9, 12, 13) are effective, allowing to decrease postprandial hyperglycaemia and, consequently, insulin release (9). Plasmapheresis, chemotherapy, or glucocorticoid therapy are required in rare cases (such as myeloma) (5). Nevertheless, there have been cases where patients were even treated with surgery (partial pancreatectomy) due to the physicians' poor knowledge of IAS (14, 15).

IAS should be differentiated from another form of autoimmune hypoglycaemic syndrome, type B insulin resistance. This disease is caused by stimulation of insulin receptors by antibodies (rI-Ab). The exact prevalence of this disease is unknown (16); the literature describes approximately 50 such patients in total (12). The disease is usually found in women with other autoimmune disorders (most commonly SLE); besides, it occurs as a manifestation of a paraneoplastic syndrome in patients with multiple myeloma or Hodgkin's disease. African Americans are more frequently affected (17).

Patients with this syndrome are usually erroneously diagnosed with type 2 diabetes mellitus (18), less frequently with type 1 diabetes (19), as hyperglycaemia is often observed at the onset of the disease. *Acanthosis nigricans* in the axillary and inguinal regions, the neck, around the eyes (17), and around the mouth (14) is a typical, frequently seen feature of this condition. Laboratory tests reveal significantly (more than 200 μU/mL) elevated insulin levels and normal triglyceride concentrations (in contrast to other insulin resistance syndromes) (17). Women often have enlarged ovaries and elevated testosterone levels.

Table 2 Examination at the local facility.

	December 28, 2017*	January 09, 2017*	January 29, 2018*	February 2018†	Reference interval
Insulin, pmol/L	>4167	>4167	3634	809	16.0–183.3
Glucose, mmol/L	4.2	3.85	4.24	4	<6.1[a]; 3.89–5.83[b]
HbA1C, %	5.4				4-6
C-peptide, nmol/L			1.379	0.755	<1.73[c]; 0.4–1.5[d]
Proinsulin, pmol/L			9.16	6.1	<4.3

*After overnight fast; †After prolonged fasting test; [a]Reference interval <6.1 refers to analysis of December 28, 2017; [b]Reference interval of 3.89-5.83 refers to other analyses; [c]Reference interval <1.73 refer to analysis of January 29, 2018; [d]Reference interval 0.4-1.5 refers to analysis of February 2018.

ID: 19-0159; June 2020
DOI: 10.1530/EDM-19-0159

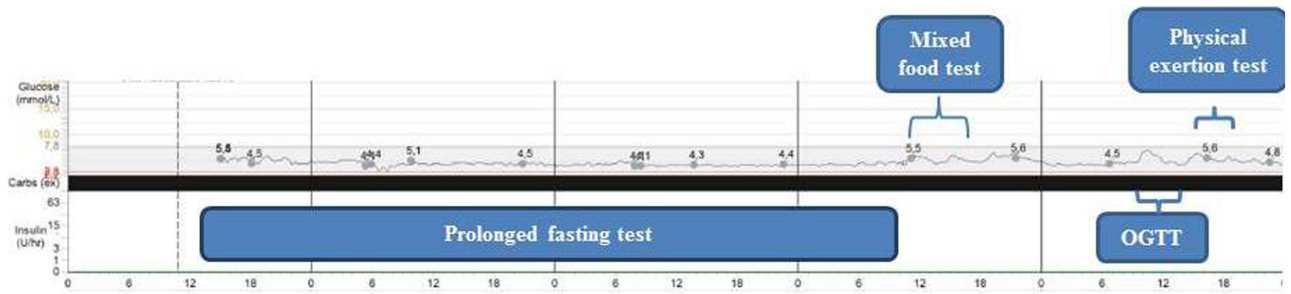
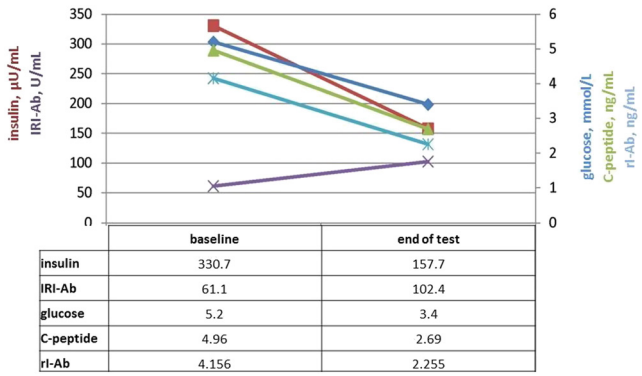


Figure 1
Tests with 72-h fast, mixed food, physical exertion, and OGTT performed using a continuous blood glucose monitoring system with a portable device (at the Endocrinology Research Centre).

According to Arioglu *et al*., one-third of patients with type B insulin resistance develop a spontaneous remission within 11–48 months. Otherwise, the patient requires pharmacological therapy (hypoglycaemia should be treated with glucocorticoids, cyclosporin A, azathioprine, cyclophosphamide, mycophenolate mofetil, and rituximab (17, 18, 19, 20, 21); besides, some patients are treated with plasmapheresis (17, 18, 19)); however, a remission can be achieved only in 50% of cases (17). Mortality rates are high (18): up to 54% of patients die within 10 years after diagnosis (21). The unfavourable prognosis is both due to the underlying condition and severe hypoglycaemic episodes (19).

In 2017, Kuznetsova *et al*. made the first Russian description of a case of IAS in a 3.5-year-old Caucasian girl, which was possibly caused by a previous course of pyritinol therapy. The authors pointed to the need of inclusion of IAS in the differential diagnosis of hypoglycaemic syndrome (after excluding iatrogenic hypoglycaemias and organic hyperinsulinism) in all patients with atypical clinical presentation combined with extremely high insulin levels and anti-insulin autoantibodies forming without previous insulin therapy (22).



	baseline	end of test
insulin	330.7	157.7
IRI-Ab	61.1	102.4
glucose	5.2	3.4
C-peptide	4.96	2.69
rI-Ab	4.156	2.255

Figure 2
Prolonged fasting test (at the Endocrinology Research Centre). Reference values: glucose: 3.1–6.1 mmol/L; insulin: 16.0–183.3 pmol/L; C-peptide: 0.4–1.5 nmol/L; IRI-Ab: <10 U/mL; rI-Ab: <3.65 ng/mL.

Case presentation

Patient A, female, 46 years old, was evaluated at the Endocrinology research Centre in April 2018. The patient reported episodes of dizziness, sense of fear, and 'creeping' sensations occurring 2–3 h after meals and associated with blood glucose reductions to a minimum 2.1 mmol/L. The patient's medical history revealed that these attacks first developed in December 2017, a week after discontinuation of alpha-lipoic acid (the patient received this drug for polyneuropathy of the lower limbs in November 2017). The last attack occurred at the February 2018.

The patient was examined several times at her local facility (Table 2): blood tests performed after an overnight fast revealed no evidence of hypoglycaemia; however, a significant increase in insulin levels and a moderate elevation of proinsulin were observed. In February 2018, the patient underwent a prolonged fasting test, which was discontinued after 72 h since the blood glucose concentrations were normal. A significant increase in insulin levels was also

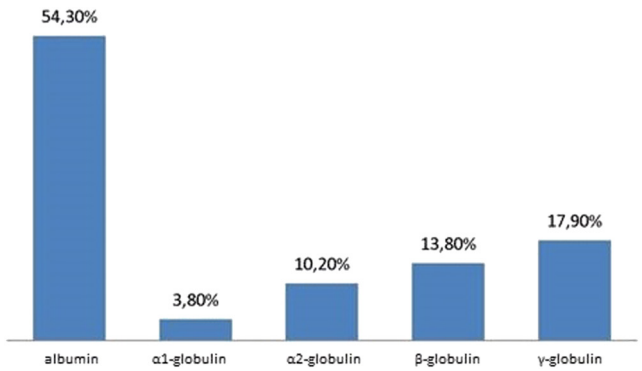


Figure 3
Serum protein electrophoresis.

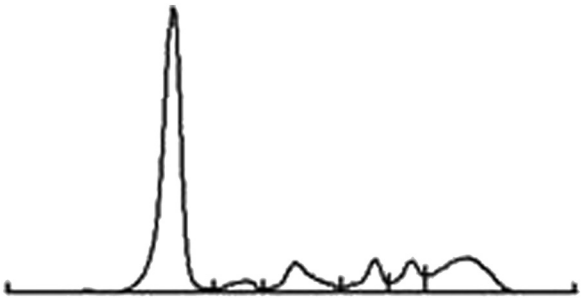


Figure 4
Serum protein electrophoresis.

observed after the test, but IRI-Ab and rI-Ab levels were still not measured. As insulinoma was suspected, abdominal ultrasonography and MRI were performed and demonstrated no evidence of a mass lesion in the pancreas.

Concomitant diseases included grade II obesity (BMI 36.0 kg/m^2), dyslipidaemia, hyperuricaemia, cholelithiasis, hiatal hernia, and mixed gastritis (superficial and erosive). In 2016, the patient had surgery (removal of the uterus and ovaries) for bilateral contained pyosalpinx, ovarian abscess, and endomyometritis. Besides, in September 2017, the patient had surgery for discitis, which was followed by a 2-month antibacterial therapy that included Ciprofloxacin, Doxycycline, and Metronidazole. There is no family history of autoimmune diseases.

In April 2018, the patient was first evaluated at the Endocrinology Research Centre. Physical examination revealed no signs of hyperandrogenism or *acanthosis nigricans* (the serum testosterone level was also within the reference interval).

Investigation

A continuous blood glucose monitoring system with a portable device was used to perform provocation tests with a 72-h fast (Figs 1 and 2), mixed food, physical exertion (23), and an oral glucose tolerance test (OGTT), which revealed no hypoglycaemia. However, the tests revealed significant increases in insulin and IRI-Ab both at the start and at the end of the prolonged fasting test, as well as pronounced insulin resistance (HOMA-IR = 76); HOMA was calculated using the following formula: insulin (μU/mL) × glucose (mmol/L)/22.5. They also showed a moderate increase in rI-Ab at the start of the test and normal levels at its completion.

Table 3 Serum protein immunochemistry.

Test	Value	Units	Reference interval
IgG, IU/mL	192	IU/mL	95–235
IgA, IU/mL	290	IU/mL	55–250
IgM, IU/mL	183	IU/mL	60–405
κ/λ	2.2	-	1.1–2.9
Cryoglobulins	negative	-	negative
κ-FLC[1], mg/L	11.7	mg/L	3.3–19.4
λ-FLC, mg/L	15.3	mg/L	5.7–26.3
κ/λ-FLC	0.76	-	0.26–1.65

[1]Free light chains.

Table 4 HLA-typing.

HLA-DRB1*03
HLA-DQA1*05:01
HLA-DQB1*02
HLA-DRB1*04
HLA-DQA1*03:01
HLA-DQB1*03:02

IAS was thus suspected based on the IRI-Ab increase. The lack of evidence of hypoglycaemic syndrome at the time of examination was most probably due to the reduced IRI-Ab level long after discontinuation of a drug containing a sulfhydryl group.

After that, clinical workup was started to exclude multiple myeloma and monoclonal gammopathy, two possible causes of elevated IRI-Ab. The total protein, calcium, creatinine concentrations, and complete blood count results were within reference intervals. Serum and urine immunochemistry with free light chain determination (Figs 3 and 4) was performed and revealed no pathological gradients or abnormal free light chain ratios. Serum protein electrophoresis results (Table 3) revealed an increase in polyclonal IgA, whereas the concentrations of other immunoglobulins were found to be within reference intervals. Concentrated urine protein tests demonstrated traces of albumin and no Bence-Jones protein (including highly sensitive immunofixation analysis). Therefore, no evidence of multiple myeloma or monoclonal gammopathy was obtained.

Additionally, in view of the IRI-Ab increase, we performed HLA-typing and revealed DRB1*03-DQA1*05:01-DQB1*02/DRB1*04-DQA1*03:01-DQB1*03:02 genotype (Table 4). The presence of a DRB1*04 allele in a high-risk haplotype was shown, which is consistent with data reported by most authors. However, as high-definition genotyping of DRB1 alleles was not carried out, the specific DRB1*04 allele is unknown. DRB1*03 detected in IAS has already been reported in a publication (24).

Therefore, the medical history data (association between hypoglycaemia episodes and use of thioctic acid) and results of laboratory and genetic tests led to the diagnosis of IAS induced by a drug containing a sulfhydryl

ID: 19-0159; June 2020
DOI: 10.1530/EDM-19-0159

Table 5 Immunological tests.

Test	Value	Units	Reference interval
Antibodies to 21-hydroxylase	0.028	U/mL	<0.4
Antibodies to thyroid peroxidase (TPO)	0.8	IU/mL	0–5.6
Abnormalities to thyroglobulin (TG)	10	IU/mL	0–115
Antibodies to thyroid-stimulating hormone receptor (rTSH)	0.3	IU/L	0–1.75
Antibodies to pancreatic glutamic acid decarboxylase	0.3	U/mL	0–1
Antibodies to pancreatic islet cells	0.23	U/mL	0–1
Antibodies to tyrosine phosphatase	0.6	U/mL	0–10
Antibodies to zinc transporter	10	U/mL	0–15

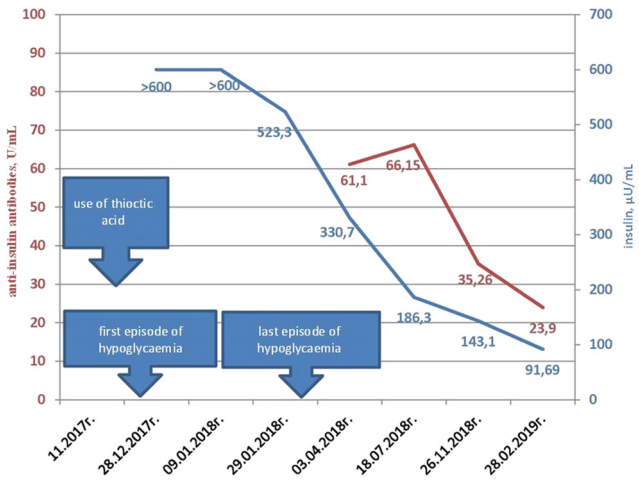


Figure 5
Changes in insulin and IRI-Ab levels over time.

group (alpha-lipoic acid). Type B insulin resistance was ruled out based on the minor increase in rI-Ab and the absence of hyperandrogenism and *acanthosis nigricans*.

As the patient was diagnosed with IAS, she underwent immunological examination to exclude a predisposition to other autoimmune disorders of the endocrine system: adrenal insufficiency, autoimmune thyroid disorders, and diabetes mellitus (Table 5). As the table shows, levels of all evaluated antibodies were within reference intervals. Although the levels of antibodies to TPO, TG, and rTSH were not increased, thyroid ultrasonography demonstrated signs of autoimmune damage. Follow-up was recommended in view of a normal TSH level (1.39 µIU/mL).

Treatment

The patient was also advised to avoid (unless vitally indicated) using drugs that can potentially trigger formation of IRI-Ab. No drug therapy was administered for IAS and no dietary adjustment was used either, as the syndrome had resolved spontaneously. Recommendations included blood glucose determination with a blood glucose monitor when the patient felt unwell.

Outcome and follow-up

Episodes of hypoglycaemia did not recur within 10 months after discharge from the hospital. A follow-up evaluation performed after an overnight fast revealed a gradual reduction in the levels of insulin and IRI-Ab (Fig. 5 and Table 6) and decreased insulin resistance (HOMA-IR = 31). Follow-up of the patient continues.

Discussion

Therefore, IAS should be ruled out in all patients with hyperinsulinaemic hypoglycaemia to facilitate further determination of an adequate strategy of clinical evaluation, treatment, and follow-up. Diagnosis of this condition requires detailed interview on the use of implicated drugs and careful analysis of the clinical findings and laboratory test results. Pancreatic imaging is not required in patients with IAS. It should also be taken into consideration that autoimmune hypoglycaemia

Table 6 Test results obtained after discharge from the Endocrinology Research Centre after an overnight fast.

	July 18, 2018	November 26, 2018	February 28, 2019	Reference interval
Insulin, pmol/L	1293.75	993.75	636.74	16.0–183.3
Glucose, mmol/L	4.89	4.87	5.63	3.1–6.1
C-peptide, nmol/L	1.37	1.63	1.49	0.4–1.5
IRI-Ab, U/mL	66.15	35.26	23.9	<10
rI-Ab, ng/mL	4.94	0.823	0.238	<3.65

may be the first manifestation of severe haematological and autoimmune diseases, and therefore patients in this cohort should undergo in-depth evaluation.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
Funded by a grant from the Russian Science Foundation (project 17-75-30035).

Patient consent
Wrtitten informed consent has been obtained from the patient for the publication of this article.

Author contribution statement
Yukina Marina, Nuralieva Nurana, Solovyev Maksim, Troshina Ekaterina, and Vasilyev Evgeny performed case study and wrote the article.

References

1 Li JK, Lee WK, Chan CH, Ng R & Wong BK. Auto-insulin antibodies due to methimazole in a patient with Myasthenia Gravis and Graves disease. *Annals of Gerontology and Geriatric Research* 2015 **2** 1021–1022.
2 Rouabhia S, Ramanoelina J, Godmer P, Reach G, Dutel JL & Guillevin L. Insulin autoimmune syndrome revealing systemic lupus erythematosus. *Annales de Medecine Interne* 2003 **154** 59–60.
3 Censi S, Mian C & Betterle C. Insulin autoimmune syndrome: from diagnosis to clinical management. *Annals of Translational Medicine* 2018 **6** 335. (https://doi.org/10.21037/atm.2018.07.32)
4 Lichtman MA & Balderman SR. Unusual manifestations of essential monoclonal gammopathy. II. Simulation of the insulin autoimmune syndrome. *Rambam Maimonides Medical Journal* 2015 **6** e0027. (https://doi.org/10.5041/RMMJ.10212)
5 Zhang Y & Zhao T. Hypoglycemic coma due to insulin autoimmune syndrome induced by methimazole: a rare case report. *Experimental and Therapeutic Medicine* 2014 **8** 1581–1584. (https://doi.org/10.3892/etm.2014.1964)
6 Zeng XX, Tang YL, Hu KX, Wang J, Zhu LY, Liu JY & Xu J. Insulin autoimmune syndrome in a pregnant female: a rare case report. *Medico* 2017 **96** 1–5. (https://doi.org/10.1097/MD.0000000000009213)
7 Ismail AAA. The insulin autoimmune syndrome (IAS) as a cause of hypoglycaemia: an update on the pathophysiology, biochemical investigations and diagnosis. *Clinical Chemistry and Laboratory Medicine* 2016 **54** 1715–1724. (https://doi.org/10.1515/cclm-2015-1255)
8 Gullo D, Evans JL, Sortino G, Goldfine ID & Vigneri R. Insulin autoimmune syndrome (Hirata Disease) in European Caucasians taking α-lipoic acid. *Clinical Endocrinology* 2014 **81** 204–209. (available at: https://www.ncbi.nlm.nih.gov/pubmed/24111525) (https://doi.org/10.1111/cen.12334)
9 Rajpal A, Kassem LS, Moscoso-Cordero M & Arafah BM. Clopidogrel-induced insulin autoimmune syndrome: a newly recognized cause of hypoglycemia in a patient without diabetes. *Journal of the Endocrine Society* 2017 **1** 1217–1223. (https://doi.org/10.1210/js.2017-00316)
10 Malek R, Chong AY, Lupsa BC, Lungu AO, Cochran EK, Soos MA, Semple RK, Balow JE & Gorden P. Treatment of Type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3641–3647. (https://doi.org/10.1210/jc.2010-0167)
11 Arzamendi AE, Rajamani U & Jialal I. Pseudoinsulinoma in a white man with autoimmune hypoglycemia due to anti-insulin antibodies value of the free C-peptide assay. *American Journal of Clinical Pathology* 2014 **142** 689–693. (https://doi.org/10.1309/AJCPX56JQBJHUBGJ)
12 Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK & Gorden P. Autoimmune forms of hypoglycemia. *Medicine* 2009 **88** 141–153. (https://doi.org/10.1097/MD.0b013e3181a5b42e)
13 Wong SL, Priestman A & Holmes DT. Recurrent hypoglycemia from insulin autoimmune syndrome. *Journal of General Internal Medicine* 2014 **29** 250–254. (https://doi.org/10.1007/s11606-013-2588-9)
14 Masjhur JS. Insulin autoimmune syndrome (Hirata's disease): severe hypoglycemic episodes in Graves' hyperthyroidism patient treated with methimazole. *Acta Medica Indonesiana* 2005 **37** 214–217.
15 Uchigata Y & Hirata Y. Insulin autoimmune syndrome (Hirata disease). In *Immunoendocrinology: Scientific and Clinical Aspects*, pp. 343–368. Ed Eisenbarth. Humana Press, 2011.
16 Orphanet: the portal for rare diseases and orphan drugs. [Internet]. (available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=2298)
17 Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI & Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. *Medicine* 2002 **81** 87–100. (https://doi.org/10.1097/00005792-200203000-00001)
18 Viswanathan L & Sirisena I. Immunosuppressive therapy in treatment of refractory hypoglycemia in Type B insulin resistance: a case report. *Journal of the Endocrine Society* 2017 **1** 1435–1439. (https://doi.org/10.1210/js.2017-00292)
19 Shanker K, Daley T, Semple R, Rouster-Stevens K & Ham JN. Intractable hypoglycemia in the setting of autoimmune overlap syndrome. *Pediatrics* 2017 **139** e20160866. (https://doi.org/10.1542/peds.2016-0866)
20 Chon S, Choi MC, Lee YJ, Hwang YC, Jeong IK, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, *et al*. Autoimmune hypoglycemia in a patient with characterization of insulin receptor autoantibodies. *Diabetes and Metabolism Journal* 2011 **35** 80–85. (https://doi.org/10.4093/dmj.2011.35.1.80)
21 Malek R, Chong AY, Lupsa BC, Lungu AO, Cochran EK, Soos MA, Semple RK, Balow JE & Gorden P. Treatment of Type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 3641–3647. (https://doi.org/10.1210/jc.2010-0167)
22 Kuznetsova ES, Pilipenko OV & Melikyan MA. Insulin autoimmune syndrome: a rare cause of hypoglycemia. The case report of the syndrome in pediatric practice. *Problems of Endocrinology* 2017 **63** 189–194. (https://doi.org/10.14341/probl2017633189-194)
23 Gama R, Teale JD & Marks V. Best practice no 173: clinical and laboratory investigation of adult spontaneous hypoglycaemia. *Journal of Clinical Pathology* 2003 **56** 641–646. (https://doi.org/10.1136/jcp.56.9.641)
24 Sahni P, Trivedi N & Omer A. Insulin autoimmune syndrome: a rare cause of postprandial hypoglycemia. *Endocrinology, Diabetes and Metabolism Case Reports* 2016 **2016** 16-0064. (https://doi.org/10.1530/EDM-16-0064)

Received in final form 14 April 2020
Accepted 28 April 2020