



Exogenous insulin autoimmune syndrome: A case report and review of literature

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Abstract

BACKGROUND

Insulin autoimmune syndrome (IAS) is a severe manifestation of spontaneous hypoglycemia. It is characterized by elevated levels of immune-reactive insulin and highly potent insulin autoantibodies (IAAs), which are induced by endogenous insulin circulating in the bloodstream. It is distinguished by recurring instances of spontaneous hypoglycemia, the presence of IAA within the body, a substantial elevation in serum insulin levels, and an absence of prior exogenous insulin administration. Nevertheless, recent studies show that both conventional insulin and its analogs can induce IAS episodes, giving rise to the notion of non-classical IAS. Therefore, more attention should be paid to these diseases.

CASE SUMMARY

In this case report, we present a rare case of non-classical IAS in an 83-year-old male patient who present with symptoms of a psychiatric disorder. Upon symptom onset, the patient exhibited Whipple's triad (including hypoglycemia, blood glucose level less than 2.8 mmol/L during onset, and rapid relief of hypoglycemic symptoms after glucose administration). Concurrently, his serum insulin level was significantly elevated, which contradicted his C-peptide levels. After a comprehensive examination, the patient was diagnosed with exogenous insulin autoimmune syndrome. Considering that the patient had type 2 diabetes mellitus and a history of exogenous insulin use before disease onset, it was presumed that non classical IAS was induced by this condition. The PubMed database was used to search for previous cases of IAS and non-classical IAS to analyze their characteristics and treatment approaches.

CONCLUSION

The occurrence of non-classical IAS is associated with exogenous insulin or its analogs, as well as with sulfhydryl drugs. Symptoms can be effectively alleviated through the discontinuation of relevant medications, administration of hormones or immunosuppressants, plasma exchange, and lifestyle adjustments.

Key Words: Insulin autoimmune syndrome; Type 2 diabetes; Exogenous insulin; Insulin autoantibodies; Hypoglycemia; Case report

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Core Tip: Exogenous insulin autoimmune syndrome (EIAS), also known as non-classical insulin autoimmune syndrome, occurs in individuals with type 2 diabetes who use exogenous insulin, resulting in the production of insulin autoantibodies and the subsequent development of hyperinsulinemia. This condition is characterized by significant fluctuations in blood glucose levels and insulin resistance. In patients with type 2 diabetes receiving treatment with oral medications or insulin therapy, episodes of hypoglycemia are often attributed to drug-related causes. Consequently, EIAS tends to be overlooked in clinical practice, particularly among elderly patients. Herein, we report a case of EIAS in an elderly person. Based on an analysis of PubMed cases, it has been observed that the disease tends to be self-limiting with a favorable prognosis.

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INTRODUCTION

The insulin autoimmune syndrome (IAS) is a rare clinical condition that often leads to misdiagnosis or missed diagnosis. Although its exact etiology remains unclear, several studies have suggested a strong association between genetic susceptibility and the use of sulfhydryl-containing drugs or exogenous insulin. In clinical practice, both IAS and exogenous insulin autoimmune syndrome (EIAS) present with hypoglycemic symptoms and positive insulin antibodies[1]; however, they differ in terms of the inducing factors and characteristics of the insulin antibody[2]. The prognoses for both IAS and EIAS are generally favorable, with treatment goals focused on correcting hypoglycemia, addressing underlying causes, and reducing insulin antibody titers[3].

CASE PRESENTATION

Chief complaints

The patient, an 83-year-old man, was admitted to the hospital due to episodic nocturnal gibberish for 3 d and worsening for 1 d.

History of present illness

A member of his family acted as a proxy and provided an account of the patient's symptoms during the episodes which included: incoherent speech, slurred words, bilateral drooling, and impaired recognition of family members, lasting for approximately 20 min. The symptoms ameliorated following sleep, and partial recollection was observed upon awakening. At approximately 4:00 on the same day, the above symptoms recurred.

History of past illness

The patient had a medical history of hypertension, managed through the long-term use of sustained-release nifedipine and candesartan tablets for treatment. He was diagnosed with type 2 diabetes over 20 years ago. Initially, oral hypoglycemic drugs were prescribed to manage blood glucose levels. However, 3 months ago, owing to inadequate glycemic control, the patient was initiated on insulin aspart injections before meals at a dose of 8 units in the morning, 10 units at noon, and 10 units in the evening. The subcutaneous administration of insulin glargine was initiated at a dose of 10 units at 20:00. Unfortunately, specific details regarding blood glucose control are unavailable as the patient did not monitor their blood glucose levels at home. Moreover, the patient's medical history included chronic bronchitis, old cerebral infarction, hepatitis B, benign prostatic hyperplasia, and left knee arthritis.

Personal and family history

The patient denied any specific family history.

Physical examination

Physical examination revealed a body temperature of 36.3 °C, respiratory rate of 19 times/minute, pulse rate of 76 times/min, blood pressure of 130/75 mmHg, SPO2 level of 99% (with oxygen supplementation), height of 170 cm, weight of 70 kg, and body mass index of 24.22 kg/m². His random blood glucose level on admission was 13 mmol/L. No significant abnormalities were detected during cardiovascular or abdominal examinations, and no edema was observed in either lower limb. Neurological examinations did not reveal any apparent abnormalities.

Laboratory examinations

Complete blood count, thyroid function test, plasma ammonia, coagulation profile, liver and kidney function tests, electrolytes, B-type natriuretic peptide, cardiac enzyme spectrum, three indicators of myocardial infarction urinalysis and routine stool examination, glomerular filtration rate, rheumatoid factor test, and autoimmune liver disease antibody levels were within normal ranges. Serum cortisol levels at 8:00 and 16:00 were also within normal limits. Tumor markers including alpha-fetoprotein, carbohydrate antigen 125, carbohydrate antigen 19-9, total prostate-specific antigen, neuron-specific enolase, cytokeratin fragment 19 and cancer antigen 72-4 were all normal except for carcinoembryonic antigen which was elevated (6.15 ng/mL, reference value: 0-4.00 ng/mL). His glycated hemoglobin level was 7.0%.

Imaging examinations

The patient's electrocardiogram showed normal sinus rhythm. Enhanced computed tomography of the pancreas revealed pancreatic atrophy, bilateral renal cystic lesions, and kidney stones in the right kidney. Brain diffuse-weighted magnetic resonance imaging demonstrated multiple lacunar infarctions in the brainstem, bilateral basal ganglia, and frontal and parietal lobes. There was also evidence of cerebral atrophy, white matter degeneration, and cerebral arteriosclerosis. Abdominal ultrasound indicated fatty liver and slightly increased echogenicity of the bilateral renal parenchyma with bilateral cystic lesions. The bladder wall appeared rough, with diverticulum formation. Additionally, an enlarged prostate with stones or calcified spots was identified.

Further diagnostic work-up

Around 2:00 on the day of admission, the patient presented with delirium, palpitations, and fatigue. His finger blood glucose measurement revealed a level of 2.6 mmol/L. Consequently, 20 mL glucose solution was orally administered and 10% glucose solution was intravenously infused. Hence, the blood glucose levels increased to 9.4 mmol/L. After the gradual relief of symptoms, the insulin dosage were reduced. On the second night after admission, the patient experienced another episode of palpitations and discomfort. Immediate venous blood glucose measurement showed a level of 2.7 mmol/L (reference range: 3.9-6.1 mmol/L), an insulin level of more than 600 mU/L (reference range: 8.5-22.70 mU/L), and a C-peptide level of 3.40 ng/mL (reference range: 0.78-5.19 ng/mL). This indicated an insulin-C-peptide dissociation phenomenon. The insulin and C-peptide release tests of the patient (Table 1) yielded results consistent with previous reports, suggesting an association between hypoglycemia in the patient and high serum insulin concentrations. Therefore, immediate discontinuation of insulin was implemented. Dynamic blood glucose monitoring in the patient revealed fluctuations ranging from 2.4 to 18.0 mmol/L, with episodes of low blood sugar predominantly occurring between 2:00 to 5:00, where blood sugar levels fluctuated within the range of 2.4 to 3.3 mmol/L; hence, hypoglycemia occurred intermittently. The insulin antibody (Table 2) and gene tests were completed. The human leukocyte antigen (HLA) alleles were HLA-DRB1*0803/1202, HLA-DQB1*0601/0301, HLA-DPB1*0501/0501.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was EIAS.

TREATMENT

Upon confirmation of the diagnosis, the patient was advised to discontinue insulin therapy, modify their dietary regimen to include frequent smaller meals throughout the day, and initiate oral linagliptin administration at a dose of 5 mg once daily.

OUTCOME AND FOLLOW-UP

After treatment initiation, no recurrent episodes of hypoglycemic attacks were observed in the patient; their blood glucose levels remained stable without any recurrence of psychiatric symptoms. No hypoglycemic events occurred during the 3-month follow-up.

Table 1 Findings from insulin release test and C-peptide release test

Project	0 h	2 h	After 10 d of insulin withdrawal	0 h	2 h
Insulin release test	> 600 mU/L	> 600 mU/L		> 600 mU/L	> 600 mU/L
C-peptide release test	3.60 ng/mL	4.90 ng/mL		4.90 ng/mL	6.62 ng/mL

Table 2 Insulin antibody test

Project	After 10 d of insulin withdrawal	Reference value
Islet cell antibody	0.05	0.05 < 0.9 COI
Serum anti-glutamic acid decarboxylase antibody	0.96	0.99 < 10 IU/mL
Insulin autoantibody	12.6	13.3 < 0.9 COI

DISCUSSION

IAS or Hirata's disease, was initially documented by Japanese scholars[4] and is widely recognized as a significant etiology of spontaneous hypoglycemia. IAS is a relatively uncommon condition encountered in clinical practice, with a pathogenesis characterized primarily by elevated levels of insulin autoantibodies (IAAs) and excessive endogenous insulin secretion[5]. The diagnosis of IAS can generally be confirmed if the following conditions are met[6]: Hyperinsulinemic hypoglycemia; during hypoglycemic episodes, blood glucose levels decrease below 3.0 mmol/L; increased IAA concentrations; no exogenous insulin administration was employed; and no observable pancreatic pathological abnormalities.

Research suggests that approximately half of the patients with IAS have previously been exposed to relevant medications. These medications are classified into two categories: Those containing thiol-based compounds, such as methimazole, propylthiouracil, lipoic acid, imipenem, glutathione, captopril, sulfasalazine, amphotericin B, and N-acetylcysteine, with methimazole being the most prevalent; and those not inherently containing thiol groups but with the ability to produce thiol-based compounds through metabolism, including clopidogrel, pantoprazole, rabeprazole, levofloxacin and isoniazid[7]. Thiols possess the ability to interact with disulfide bonds within insulin molecules, inducing conformational alterations in endogenous insulin and eliciting an immune response that leads to the production of IAA. These antibodies are characterized by a high binding capacity and low affinity[2], suggesting that a large amount of insulin binds to form complexes; however, this easily dissociates, resulting in increased free insulin in the circulation [8], consequently resulting in the manifestation of IAS[9].

Genetic susceptibility also plays an important role in IAS[10]. Studies have found a strong correlation between IAS and the HLA phenotype[11,12]. However, different ethnic groups carry different HLA types, among which the HLA-DR4 allele is the most common[13]. Approximately 96% of Japanese patients with IAS express HLA-DR4[14], mainly including DRB1*0406, with a few including DRB1*0403 and DRB1*0407[15]. The main HLA types in Korean population are DRB1*0803 and DRB1*1602[16], and those in European and American populations are DRB1*0403[17]. At present, there are few HLA samples for IAS gene detection in China, those that exist mainly include DRB1*0406[18] and DRB1*0406/0409[19], most of which are detected in patients with hyperthyroidism taking methimazole. The possible mechanism is that HLA-DRB1*0406 encodes serine, and when exposed to reducing substances such as methimazole, specific fragments of the insulin A chain have a high affinity for their polypeptide-binding sites, thereby stimulating the proliferation of T cell lines and resulting in increased IAA production[20]. However, in recent years, some scholars have also reported that HLA-DRB1*0415, HLA-DRB1*0404, and other genes may also be susceptibility genes for IAS[21,22]. However, there is still a lack of large-scale research data.

Furthermore, in recent years, the symptoms of hypoglycemia induced by exogenous insulin in patients with diabetes have become similar to those of IAS, leading scholars to designate this condition as EIAS, which is a non-classical form of IAS[23].

EIAS denotes that the autoimmune response is induced by exogenous insulin, resulting in the production of the immunoreactive antigen IAA. This is characterized by low insulin binding capacity and relatively high insulin affinity[2], suggesting that the amount of insulin binding to form complexes is small, and it does not easily dissociate, resulting in islet resistance[24], and elevation of serum immunoreactive insulin concentrations. These features instigate recurrent episodes of spontaneous hypoglycemia[25]. Almost all types of insulin can contribute to the occurrence of EIAS in individuals with diabetes[26,27]. Furthermore, the time interval between insulin administration and recurrent hypoglycemia can exhibit irregularities ranging from a few days to several years[26]. Owing to the adverse effects of insulin-induced hypoglycemia, EIAS is easily missed or misdiagnosed in patients with diabetes, and numerous domestic and international studies have consistently reported a wide range of detection rates for IAA in patients using exogenous insulin, varying from 21.5% to 78.0%[28]. In patients with type 2 diabetes receiving exogenous insulin therapy, if the fasting insulin/C-peptide ratio exceeds 8.6 or the postprandial 2-hour insulin/C-peptide ratio surpasses 17.8, it indicates the potential presence of IAAs in the body. A higher ratio corresponds to an increased likelihood of a positive result, thereby necessitating prompt testing for IAAs[29]. In clinical practice, when patients with type 2 diabetes undergoing

insulin therapy experience recurrent episodes of hypoglycemia, it is important to consider the possibility of EIAS. A diagnosis of EIAS can be made if there is a significant increase in serum insulin levels accompanied by a dissociation between insulin and C-peptide, along with positive results for islet cell autoantibodies, after ruling out other potential causes such as medication usage, tumors, deficiency in insulin counter-regulatory hormones, and autoimmune diseases.

Although the incidence of EIAS in clinical practice is rare, it has been progressively increasing over the years due to the escalating number of patients with diabetes and widespread utilization of insulin preparations[30]. Because of the potential for severe hypoglycemia, EIAS can be easily misdiagnosed in clinical practice; therefore, clinicians should be aware of this condition. In patients receiving insulin therapy with poor blood sugar control and frequent episodes of hypoglycemia, apart from considering factors such as insulin dosage, formulation, administration method, and dietary rhythm, it is also crucial to consider performing pancreatic islet-related antibody and glucose tolerance tests to assess insulin and C-peptide levels. Special attention should be paid to the presence of dissociation between insulin and C-peptide to promptly detect EIAS.

Currently, there is no standardized treatment protocol for EIAS. The primary focus is on the correction of hypoglycemia and the conversion of IAAs to a negative status. Measures primarily encompass discontinuation of insulin therapy, administration of glucocorticoids, immunosuppressants, and plasma exchange, among others. Furthermore, patients are encouraged to implement nutritional interventions, such as adjusting dietary structure to include smaller and more frequent meals, and selecting carbohydrates with a low glycemic index, as well as enhancing lifestyle by engaging in mild aerobic exercise and avoiding excessive physical exertion or exercising on an empty stomach. These measures exhibit a certain efficacy in alleviating symptoms[31]. The course of EIAS is typically self-limiting and has a favorable prognosis. In most patients, hypoglycemic episodes can gradually be alleviated by discontinuing insulin therapy or in combination with oral antidiabetic medications and the implementation of lifestyle modifications.

CONCLUSION

In conclusion, both classic IAS and EIAS present with hypoglycemia and elevated serum levels of IAA. However, EIAS specifically manifests as a confirmed history of exogenous insulin therapy and no history of thiol-based drug use. Our understanding of the pathogenesis and progression of both classic IAS and EIAS remains incomplete, necessitating active exploration in clinical settings to enable accurate diagnosis and targeted treatments and avoid misdiagnosis or delayed illness. Larger sample sizes are required to enhance our understanding of this disease subtype. Furthermore, evidence-based medicine should guide further diagnosis and treatment.

FOOTNOTES

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Author contributions: Xu LL wrote the manuscript; Chen JX proofread and verified the data in the manuscript; Cheng JP and Luo N screened patients and obtained clinical data and final reviewed the manuscript; All authors have read and approve the final manuscript. Xu LL summarized the data and wrote the first draft. Chen JX proof-collated the data and optimized the manuscript. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. Both Cheng JP and Luo N have played important and indispensable roles in data interpretation and manuscript preparation as the co-corresponding authors. Cheng JP conceptualized, designed, and supervised the whole process of the project. Luo N was responsible for data re-analysis and re-interpretation, table drawing and ideas refining. This collaboration between Cheng JP and Luo N is crucial for the publication of this manuscript and other manuscripts still in preparation.

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