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A Case Of Insulin Autoimmune Syndrome: Case Report And Literature Review

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Abstract

Background: Insulin Autoimmune Syndrome (IAS) is a rare cause of spontaneous hypoglycemia, characterized by the presence of insulin autoantibodies leading to episodes of hyperinsulinemic hypoglycemia. It is often associated with medication use, particularly sulfhydryl-containing drugs, and is more commonly reported in East Asian populations. The diagnosis of IAS requires a high index of suspicion, particularly in patients with recurrent hypoglycemia and no prior history of diabetes or exogenous insulin use.

Case Presentation: We report the case of a 30-year-old woman admitted with recurrent episodes of fasting and nocturnal hypoglycemia for one month, with glucose levels dropping below 3.8 mmol/L and two documented episodes of neuroglycopenic symptoms, including loss of consciousness. She had no prior history of diabetes but had been taking prednisolone, alpha-lipoic acid, and vitamin B complex without prescription. Laboratory findings revealed significantly elevated fasting insulin (21,525 pmol/L) and C-peptide (3.29 nmol/L) levels, with an insulin-to-C-peptide molar ratio of 6.5. Sulfonylurea screening was negative, and beta-hydroxybutyrate levels were low. Given the suspicion of IAS, insulin autoantibody testing was performed, confirming the diagnosis. The patient was initially managed with dietary modifications and acarbose but continued to experience hypoglycemia. Glucocorticoid therapy with prednisolone 30 mg daily was initiated, leading to glycemic stability. Azathioprine was added for long-term immunosuppression, and prednisolone was gradually tapered.

Conclusion: IAS should be considered in patients presenting with unexplained hypoglycemia and hyperinsulinemia. Early recognition and appropriate management with immunosuppressive therapy and dietary interventions can effectively control symptoms and prevent complications. This case highlights the importance of IAS awareness and contributes to the growing literature on its diagnosis and treatment.

Keywords: Insulin Autoimmune Syndrome, Hypoglycemia, Hyperinsulinemia, Insulin Autoantibodies, Immunosuppressive Therapy.

Introduction

Developing autoantibodies against endogenous insulin without having been exposed to exogenous insulin before is an uncommon occurrence in insulin autoimmune syndrome (IAS) [1]. The binding of autoantibodies to insulin causes a decrease in its clearance and the concomitant release of high quantities of insulin, leading to bouts of spontaneous hypoglycemia [1]. Autoantibodies are produced when the

immune system mistakenly views endogenous insulin or the insulin receptor as an alien entity, leading to insulin autoimmune syndrome (IAS) [2]. Complexes involving insulin and these autoantibodies are formed [3]. When bound to autoantibodies, insulin action is momentarily suppressed. A burst of active insulin is released into the circulation when the insulin-autoantibody complexes dissolve, which happens eventually [1]. Emergences of hypoglycemia may result from this abrupt rise in the amount of insulin that the body can use. Given the commonalities in the underlying mechanism of immune dysregulation, rheumatologists may come across IAS when assessing patients with various autoimmune disorders [4].

High levels of insulin autoantibodies induce insulin autoantibody syndrome (IAS), also known as Hirata illness, which is characterized by bouts of spontaneous hypoglycemia. The unusual syndrome is believed to be caused by hematological diseases, viruses (such as hepatitis C, varicella zoster, mumps, rubella, coxsackie B virus, and rubella), and medications [5]. The majority of case reports of IAS without known triggers have come from Japan, yet it has been speculated that these instances might have been caused by unidentified triggers [6]. It is now known that the medications alpha-lipoic acid and methimazole induce IAS [5].

Given its rarity and potential for severe hypoglycemia, early recognition of Insulin Autoimmune Syndrome (IAS) is essential for preventing life-threatening complications. This case highlights the importance of considering IAS in the differential diagnosis of spontaneous hyperinsulinemic hypoglycemia, particularly in patients without a history of diabetes or exogenous insulin use. A thorough diagnostic approach, including insulin autoantibody testing, is crucial for accurate diagnosis and appropriate management.

Case Presentation

A 30-year-old woman was admitted to the hospital in 2023 due to recurrent episodes of hypoglycemia persisting for one month. She had no significant past medical history but reported frequent hypoglycemic episodes throughout the day, with increased occurrence during fasting and nighttime, reaching glucose levels below 3.8 mmol/L. Additionally, she experienced two documented episodes of neuroglycopenic symptoms, primarily loss of consciousness, at another hospital.

Her medical history included a previous episode of facial nerve palsy a few months prior, for which she was prescribed prednisolone 40 mg for five days. At the time of admission, she was taking prednisolone, alpha-lipoic acid, diclofenac sodium, and vitamin B complex without a formal prescription. She had no history of smoking, alcohol consumption, or illicit drug use.

Upon admission, her vital signs were within normal limits, with a blood pressure of 130/80 mmHg. Her body mass index (BMI) was not recorded. Physical examination revealed no significant abnormalities of the cardiovascular, respiratory, or gastrointestinal systems. Neurological assessment showed normal muscle strength and tone in all limbs. Based on her clinical presentation, she was admitted for further evaluation of recurrent hypoglycemia.

Diagnostic Workup

Comprehensive laboratory investigations were performed, including blood, urine, and stool (routine and occult blood) tests, which were within normal ranges. Hepatic and renal function tests, electrolyte levels, autoimmune antibody screening, thyroid function tests, and morning cortisol levels were also unremarkable.

A supervised overnight fasting test revealed a significant drop in blood glucose to 2.1 mmol/L, with corresponding insulin and C-peptide levels markedly elevated (insulin = 21,525 pmol/L; C-peptide = 3.29 nmol/L). The molar insulin-to-C-peptide ratio was 6.5 (>1), raising suspicion of insulin autoantibody syndrome (IAS). Further investigations demonstrated negative sulfonylurea antibodies, persistently elevated proinsulin levels (>5 pmol/L), and a low beta-hydroxybutyrate level (<2.7 mmol/L), supporting the diagnosis of insulin autoimmune syndrome (IAA).

The patient was initially managed with dietary modifications, including frequent small meals with a low carbohydrate intake under the supervision of a dietitian. Acarbose 25 mg was introduced with major meals. However, despite these interventions, she continued to experience recurrent hypoglycemic episodes.

Subsequent antibody testing confirmed the diagnosis, with significantly elevated insulin levels (>21,000 pmol/L), positive insulin autoantibodies (>55 U/mL), and negative insulin receptor antibodies.

Management and Follow-Up

Given the confirmed diagnosis of insulin autoimmune syndrome, glucocorticoid therapy was initiated with prednisolone 30 mg daily. Continuous glucose monitoring (CGM) was implemented, demonstrating satisfactory glycemic stability without further hypoglycemic episodes.

The patient was discharged on prednisolone 30 mg once daily with continued dietary management. She was advised to perform regular glucose monitoring using both CGM and finger-stick blood glucose checks as needed.

Over six weeks, the prednisolone dose was tapered gradually by 5 mg increments until reaching 10 mg daily. Azathioprine 50 mg every 12 hours was introduced with liver function monitoring, and prednisolone was further reduced to 5 mg daily for a total duration of five months.

Discussion

Hyperinsulinaemic hypoglycemia occurs in very uncommon cases of IAS, also known as Hirata's illness. Hirata et al. [7] were the first to report this disease in 1970. The HLA-DR4 gene is strongly associated with this [8]. Haplogroup genotyping was unfortunately not possible for our patients owing to a lack of funding.

There is no gender bias in the presentation of IAS; patients often appear in adulthood. Although most bouts of hypoglycemia happen after absorption, some have reported that fasting and exertion may precipitate hypoglycemia [9]. Graves' disease, rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus are among the autoimmune disorders often linked to IAS. There was no history of any other autoimmune illness in either of our patients.

Prior to the onset of hypoglycemia, the majority of patients also experience medication exposure. Methicillin, carbimazole, glutathione, tiopronin, interferon-α, captopril, diltiazem, hydralazine, procainamide, isoniazid, D-penicillamine, imipenem, and penicillin G are among the often implicated medications [10]. Another well-known dietary supplement, alpha-lipoic acid, has also been associated with IAS [11]. Using proton pump inhibitors may cause hypoglycemia, according to another case report from our institution [12].

It is widely believed that elevated levels of insulin autoantibodies (IAA) are the underlying cause of hypoglycemia in IAS. Following consumption of meals, insulin levels rise in response to the subsequent spike in blood glucose. The ineffectiveness of insulin due to its binding to IAA causes postprandial hyperglycemia. To deal with the postprandial hyperglycemia, this causes the body to produce more insulin and C-peptide. Insulin-IAA complexes store insulin; when they dissociate, the post-absorptive state experiences a persistent release of free insulin, which may cause hypoglycemia to last longer and be more severe. The haptens in the sulfhydryl group interact with insulin's disulfide bonds to increase the hormone's immunogenicity.

In order to diagnose insulin autoantibody syndrome, insulin autoantibody titres must be measured [13]. Nevertheless, a typical limitation of the majority of the commercially accessible tests is their limited ability to identify insulin autoantibodies of the immunoglobulin-G type [14]. Therefore, various classes of

autoantibodies can cause findings to be incorrectly negative [14]. To indirectly detect insulin autoantibodies, one may use polyethylene glycol (PEG) precipitation of serum, then recover insulin in the supernatant [15]. After PEG precipitation, serum total and free insulin levels vary significantly in patients suspected of having IAS [16]. Following PEG precipitation, insulin levels in IAS are often much higher than free insulin levels; in healthy controls, the inverse is true [16].

One possible indicator for the diagnosis of IAS is the insulin to C-peptide molar ratio. Though both insulin and C-peptide are released by beta cells at equal amounts, C-peptide has a half-life of 30 minutes and insulin a half-life of 5 minutes due to its quick clearance. Hence, the insulin-to-C-peptide molar ratio is below 1 in both healthy people and insulinomas [17]. In two situations when C-peptide is inhibited, namely IAS and exogenous insulin treatment, this ratio is larger than 1 [17]. Insulin to C-peptide molar ratios higher than 1 were seen in both of our patients.

Although one patient with IAS did have hyperplasia of pancreatic islets, other than that, no pancreatic pathological abnormalities have been documented [18]. Another instance of IAS was associated with the discovery of nesidioblastosis during pancreatic biopsy [19]. Within three to six months of diagnosis, the majority of cases with IAS resolve on their own [14]. We don't know how self-resolution works, although there's some indication that antibodies may wear off over time when the antigen (such the sulfhydryl medication) is removed [14]. In a study conducted by Cappellani et al., it was shown that insulin auto-antibody levels decreased in idiopathic autoimmune syndromes (IAS) caused by alpha-lipoic acid [20].

To prevent postprandial hyperglycemia and an increase in insulin, patients with intractable hypoglycemia should eat small, frequent, low-carbohydrate meals. As an adjunct, short courses of corticosteroids, such as oral prednisolone 30-60 mg, may be prescribed [21-22]. Acarbose, diazoxide, octreotide, and partial pancreatectomy are further therapeutic medications that may be used to decrease insulin autoantibody titres and limit insulin release, respectively [19–24]. Other immunosuppressants that have been tested in IAS include azathioprine, cyclophosphamide, and mycophenolate mofetil [25-26]. When steroids have failed to alleviate symptoms, a small number of patients have found relief with rituximab, an anti-CD20 monoclonal antibody [27-30].

In summary, this case highlights the importance of considering Insulin Autoimmune Syndrome (IAS) in patients presenting with unexplained hypoglycemia and hyperinsulinemia, particularly in the absence of exogenous insulin use. Early recognition and accurate diagnosis through comprehensive biochemical and immunological testing are essential to prevent misdiagnosis and inappropriate treatment. While dietary modifications and acarbose may provide initial glycemic control, immunosuppressive therapy with glucocorticoids and azathioprine remains the mainstay of treatment for persistent or severe cases. Continuous glucose monitoring is crucial for managing fluctuations and assessing treatment efficacy. As IAS remains a rare but significant cause of hypoglycemia, increasing clinical awareness and further research are necessary to optimize diagnostic strategies and therapeutic approaches.

Conclusion

In conclusion, this case underscores the importance of considering insulin autoimmune syndrome (IAS) in the differential diagnosis of recurrent hypoglycemia, particularly in patients with no prior history of diabetes or exogenous insulin use. The markedly elevated insulin and C-peptide levels, alongside a high insulin-to-C-peptide molar ratio and positive insulin autoantibodies, were key diagnostic findings. Immunosuppressive therapy with glucocorticoids and azathioprine, combined with dietary modifications and continuous glucose monitoring, proved effective in stabilizing blood glucose levels and preventing further hypoglycemic episodes. Early recognition and appropriate management of IAS are crucial in preventing severe neuroglycopenic complications and improving patient outcomes.

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