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Hirata – Is Not a Peaceful Rice Paddy

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ABSTRACT

Background:

Insulin autoantibodies are an uncommon cause of non-diabetic hypoglycaemia in people who have never been exposed to insulin before. This condition is called Insulin Autoimmune Syndrome (IAS), or Hirata's Disease. Because of increased clinical awareness, instances are increasingly being found in various populations, although being more frequently reported in East Asian nations.

Case Presentation:

We describe two cases of middle-aged women, a 45-year-old homemaker and a 38-year-old nurse, who had low random blood glucose levels (35–59 mg/dL), giddiness, sweating, weariness, and tremors as symptoms of recurrent postprandial hypoglycaemia. Both received baseline blood tests and systemic checks that were normal. The results of the investigations showed significantly higher levels of C-peptide (1772 and 9782 pmol/L), insulin autoantibody titers (>100 and >200), and serum insulin (>1000 µU/mL). Both patients had a history of taking multivitamins that contained the known trigger alpha-lipoic acid. Hypoglycaemic episodes continued even after dietary changes and steroid treatment, although rituximab treatment produced long-lasting clinical improvement.

Discussion:

IAS is a rare but crucial differential diagnosis for hypoglycaemia that is not diabetic, particularly in individuals who are not receiving insulin therapy. It has been determined that alpha-lipoic acid frequently acts as a precipitating agent. Similar to findings in steroid-refractory cases reported by Batra et al., our patients showed conventional biochemical characteristics of IAS and reacted positively to rituximab, in accordance with earlier investigations. Prolonged morbidity and needless investigations can be avoided with early detection and awareness of IAS.

Conclusion:

Patients with increased insulin levels and spontaneous hypoglycaemia should be evaluated for IAS, especially if exogenous insulin is not being used. Effective care requires a high index of suspicion, triggering agent identification, and customized treatment, including immunosuppressive medication like rituximab.

INTRODUCTION

Autoantibodies against endogenous insulin in people who have never been exposed to exogenous insulin before are an uncommon cause of spontaneous hypoglycaemia known as Insulin Autoimmune Syndrome (IAS), or Hirata's Disease. First described by Hirata in Japan in 1970, IAS is more commonly reported in East Asian populations but remains extremely rare in India and other Western countries [1]. Usually seen in people without a history of diabetes, the syndrome manifests as postprandial hypoglycaemia with occasional hyperglycaemia. Although the precise cause is unknown, several medications, especially those with sulfhydryl groups like alpha-lipoic acid, are known to cause the autoimmune reaction in people who are genetically predisposed [2].

Clinical presentation and laboratory results, such as high titres of insulin autoantibodies in the absence of

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exogenous insulin usage and higher levels of C-peptide and insulin, are used to make the diagnosis. Depending on the severity, treatment options vary, from immunosuppressive medicine in refractory instances to dietary changes and stopping triggering chemicals [5]. In this case study, we describe two middle-aged women without diabetes or other comorbidities who experienced symptomatic hypoglycaemia as a result of IAS. After corticosteroids failed to alleviate their symptoms, they needed immunosuppressive treatment with rituximab.

Clinical case

- **Insulin Antibody Syndrome (IAS) / Hirata's Disease** is a rare cause of non-diabetic hypoglycaemia.
- Two patients, Mrs. ABC, a 38-year-old nurse, and Mrs. XYZ, a 45-year-old homemaker, both without any known comorbidities, presented with fatigue, recurrent episodes of sweating, hunger, tremor, giddiness, and palpitations.
- Their random blood sugar levels were between 35–59 mg/dL, with most episodes occurring approximately two hours postprandially and occurring up to three times daily.
- Both had normal general and systemic examinations, with routine blood tests within normal limits.
- GRBS monitoring revealed consistent postprandial hypoglycaemia, with some early morning episodes.
- Laboratory investigations showed significantly elevated insulin (>1000) and C-peptide levels (1772 and 9782), along with high insulin antibody titres (>100 and >200).
- Despite small, frequent mixed meals, hypoglycaemic episodes persisted, although with reduced frequency.
- Mrs. ABC and Mrs. XYZ had no known precipitating factors; however, both had a history of multivitamin use, including alpha-lipoic acid.
- Upon discontinuation and monitoring in the ward, clinical improvement was noted. Steroid trials were ineffective in both patients, but treatment with rituximab led to clinical improvement.

DISCUSSION

Hirata's illness, also known as Insulin Autoimmune Syndrome (IAS), is a rare but significant cause of hyper-insulinemic hypoglycaemia in individuals not receiving exogenous insulin. It is characterised by high titres of insulin autoantibodies that cause irregular insulin release and unpredictable glycaemic swings. While more common in East Asian countries, particularly Japan, reports from India and the West are increasing due to better awareness and diagnostic tools. [1,2] HLA-restricted autoimmune disease (DRB1*04 subtypes) with environmental triggers; not a tumour or monogenic disorder. [3,4]

In this case, both patients were middle-aged women with recurrent postprandial hypoglycaemia, no diabetes, and no insulin use. They had markedly elevated insulin autoantibody titres along with high C-peptide and insulin levels, consistent with previous reports in Indian IAS patients [5]. IAS can present in adulthood, with episodes often occurring in the post-absorptive state, though fasting and exercise may also trigger symptoms [6]. It is sometimes associated with autoimmune disorders such as Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis, but our patients had no such history.

Alpha-lipoic acid, a health supplement containing sulfhydryl groups, is a recognised trigger for IAS [7]. These groups may impair immune tolerance and increase insulin autoantibody synthesis in genetically susceptible individuals [2]. Both patients had taken multivitamins containing alpha-lipoic acid prior to symptom onset. Similar associations have been documented by Censi et al. (2018), where discontinuation of the suspected agent improved symptoms [2]. In our cases, hypoglycaemia persisted despite stopping alpha-lipoic acid, though dietary changes provided partial relief.

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Corticosteroids are considered first-line immunosuppressive therapy for IAS, with rituximab showing promise in steroid-refractory cases. In line with Batra et al. (2021) [9], our patients responded well to rituximab, achieving long-term clinical improvement.

Although IAS can resolve spontaneously, persistent or severe cases require treatment tailored to the cause and symptom severity. Diagnosis should be based on:

• Documented spontaneous or postprandial hypoglycaemia

• Very high insulin levels with insulin-to-C-peptide ratio >1

• Positive insulin autoantibodies (IAA)

• No prior insulin use

• Exclusion of insulinoma or islet-cell disease via imaging

• Negative sulfonylurea screen

Early recognition is crucial to prevent misdiagnosis, unnecessary testing, and prolonged morbidity. Management should address underlying triggers, with steroids or immunosuppressants reserved for more severe disease.

Despite rituximab's positive results in steroid-refractory IAS, a number of factors limit its use. Due to the drug's high cost, limited availability in public health systems, and requirement for hospital-based intravenous administration, access is restricted in many low- and middle-income nations. Off-label autoimmune indications like IAS may not be covered by insurance or government subsidies, even in situations where rituximab is accessible [9].
Hepatitis B virus (HBV) reactivation or latent TB, late-onset neutropenia, infusion-related responses, and a heightened vulnerability to opportunistic infections as a result of chronic B-cell depletion are among the risks [10]. The majority of the evidence for rituximab's safety in IAS comes from case reports and limited series, and there are no long-term safety data available.

Comparison with other causes of hypoglycaemia

Feature	IAS (autoimmune)	Type B insulin-receptor Ab syndrome (autoimmune)	Insulinoma (tumour)	Factitious hypoglycaemia (surreptitious)
Pathogenesis	IAA bind/release insulin, causing post-prandial or fasting hypoglycaemia	**Anti-INSR** antibodies; usually severe insulin resistance & hyperglycaemia, but rare hypoglycaemia phenotypes occur	β-cell neuroendocrine tumour secreting insulin autonomously	Exogenous insulin or sulfonylurea ingestion
Key genetics	**HLA-DRB1*04:06 / 04:03 enrichment*; drug triggers (α-lipoic acid, methimazole)	Autoimmunity; **no fixed germline** variant; associated autoimmune diseases common	**Somatic YY1 p.T372R** (~15–32%); **MEN1** germline in familial cases; other NET pathways variably involved	**None** (behavioural/psychiatric etiology)

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Autoantibodies	**Insulin autoantibodies (IAA) positive**	**Insulin-receptor (INSR) antibodies positive**	Negative	Negative (but may have insulin analogues detectable)
Biochemistry during event	High insulin & C-peptide; **insulin/C-peptide ratio >1** possible due to IAA kinetics	Variable; in classic TBIRS: **very high insulin with hyperglycaemia**; rare hypoglycaemia variants reported	High insulin **and** high C-peptide; proinsulin often high	If **insulin**: high insulin with **suppressed C-peptide**; if **sulfonylurea**: high insulin **and** high C-peptide with **positive drug screen**

CONCLUSION

Patients who experience frequent episodes of hypoglycaemia should be evaluated for Insulin Autoimmune Syndrome (IAS), a rare but important cause of non-diabetic hypoglycaemia, particularly when exogenous insulin usage is not present. In order to avoid needless investigations and extended morbidity, early detection and proper diagnostic evaluation—including insulin autoantibody testing—are crucial. Withdrawing triggering drugs like alpha-lipoic acid may resolve IAS, however immunosuppressive medication may be necessary in certain situations. Our examples show that in steroid-refractory IAS, rituximab may be a useful treatment option. In suitable clinical circumstances, clinicians should keep a high index of suspicion for IAS in order to facilitate prompt diagnosis and individualized treatment.

Clinical pearls

- **IAS is a rare, non-diabetic cause of hyperinsulinemic hypoglycaemia**—should be suspected in recurrent, unexplained postprandial or spontaneous episodes with elevated insulin and insulin autoantibodies.
- **HLA-DRB1*04 subtypes** are genetically associated with IAS, with environmental triggers such as **sulfhydryl-containing drugs** (e.g., alpha-lipoic acid, methimazole).
- **Alpha-lipoic acid** is a well-documented precipitant; stopping the agent can improve symptoms, though not always completely.
- **Biochemical hallmark:** very high insulin and C-peptide with **positive IAA** and absence of prior exogenous insulin exposure.
- **Diagnosis** requires exclusion of insulinoma, factitious hypoglycaemia, and other autoimmune causes (e.g., Type B insulin receptor antibody syndrome).
- **First-line therapy:** trigger withdrawal, dietary modification, and steroids; **rituximab** may be effective in steroid-refractory cases.
- **Rituximab limitations:** high cost, limited access in LMICs, intravenous administration needs, and potential serious risks including HBV reactivation, TB reactivation, late-onset neutropenia, and increased infection susceptibility.
- **Early recognition** prevents unnecessary investigations and prolonged morbidity; maintain high suspicion in patients with recurrent hypoglycaemia without insulin use.

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