# Insulin Autoimmune Syndrome

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## Introduction

Insulin autoimmune syndrome (IAS), also known as Hirata disease, was first described by Yukimasa Hirata in Japan in 1970. Disease is a rare endocrine disorder characterized by recurrent attacks of severe hypoglycaemia, characterized by elevated serum insulin, and positive insulin autoantibodies. The diagnosis is very challenging, requiring a careful workup. Early identification and diagnosis of IAS can significantly improve prognosis. Up to now, no standardized guidelines exist for the diagnosis and treatment of IAS (1).

The disease is characterized by hyperinsulinemic hypoglycaemia, elevated insulin autoantibody (IAA) titer, with no prior exposure to exogenous insulin nor pathological abnormalities of the pancreatic islets. However, recently, it has been found that insulin and its analogues can also induce IAS, and the concept of nonclassical or exogenous insulin antibody syndrome (EIAS) is defined (2).

## Epidemiology

There is no clear accepted, precise incidence for IAS, due to its rarity, the complexities of diagnosis, and limited research. While a few hundred cases were documented between 1970 and 2009, recent data is scarce. IAS is especially common in East Asian countries (more than 90% of published cases occurred in the Japanese population) (3).

## Etiology

The etiopathogenesis of IAS has not been fully understood. It is believed to involve a complex interplay of genetic predisposition and environmental actors, with autoimmune abnormalities thus leading to the production of high levels of insulin autoantibodies, which bind to insulin, disrupting insulin action and metabolism. Studies have found a strong correlation between IAS and the HLA phenotype with identified susceptibility loci, including HLA-DRB1-0406. IAA may be possibly triggered by environmental factors, including exposure to drugs, especially drugs containing sulfhydryl groups, with methimazole being the most frequently reported, and infections (4).

## Pathogenesis

The mechanism underlying the disease is mainly related to the formation of insulin–autoantibody complexes (IAA). During fasting, insulin levels are relatively low, leaving most autoantibodies unoccupied. When food is ingested and rise in blood glucose, which stimulates insulin secretion. Endogenous insulin binds to available sites on IAAs, forming insulin–autoantibody complexes. The accumulation of antibody-bound insulin in the blood impairs insulin clearance and action, resulting in hyperglycemia.

After several hours, blood glucose levels normalize, and insulin secretion decreases. Due to the low affinity of IAA for insulin causes a spontaneous dissociation of the complexes and an excess of unbound insulin, which evokes severe bouts of hypoglycaemia (4,5).

## Clinical Manifestations of IAS

Frequent attacks of Hypoglycaemia or alternating episodes of hypoglycaemia and hyperglycaemia. Hypoglycaemia may occur at any time, while typically occurs 3–5 h postprandially. Hypoglycaemia, which manifests with autonomic and neuroglycopenic symptoms, may be fatal for the patient if not treated in time. Some reported cases manifested as hypoglycaemia after repeated diabetic ketoacidosis (6).

## Diagnosis

The diagnosis of IAS is challenging, requiring a careful workup to exclude other causes of hypoglycaemia. First, confirm the diagnosis of hypoglycaemia by the Whipple triad is needed. Usually, patients affected by insulin autoimmune syndrome present with extremely high insulin concentrations, often above 1000 pmol/L, associated with elevated blood C-peptide levels during hypoglycemic episodes, indicating endogenous hyperinsulinemic hypoglycaemia. Insulin to C-peptide molar ratio: Typically, greater than 1 aid in diagnosis. The gold standard for the definitive diagnosis is the detection of IAA in a blood sample, often using polyethylene glycol (PEG) precipitation or gel chromatography. Imaging studies are obviously useless in the diagnosis. However, the difficulties in the differential diagnosis with other forms of endogenous hyperinsulinemic hypoglycemia, IAS patients often undergo expensive imaging studies in their diagnostic workup (4,7).

## Differential Diagnosis of IAS

IAS must be differentiated from all conditions that can lead to spontaneous hypoglycaemia, particularly hyperinsulinemic hypoglycemia, including insulinomas, drugs, non-insulinoma pancreatogenous hypoglycemic syndrome, and B-type insulin resistance.

## Treatment of IAS

The treatment goal for IAS patients aims to eliminate IAA from the body, and the correct and prevent hypoglycaemia. IAS is often a self-remitting disease but sometimes needs aggressive treatment in severe cases. Strategy of treatment including symptomatic treatment and specific treatment.

Symptomatic supportive treatment primarily focuses on dietary adjustments, including smaller, frequent meals (5–6 meals per day) of low glycaemic index foods and drug therapy as acarbose, to delay the absorption of glucose to prevent hypoglycaemia.

Immunosuppression therapy, glucocorticoid therapy and plasma exchange should be considered for patients whose symptoms do not resolve spontaneously after the discontinuation of causative drugs or for those who are unable to discontinue these drugs, such as patients with type 1 diabetes due to exogenous insulin-induced IAS. Also, monoclonal antibodies as Rituximab is an anti-CD20 monoclonal antibody, have been reported to be used in the treatment of severe refractory IAS cases.

Self-monitoring of blood glucose (SMBG) combined with continuous glucose monitoring systems (CGMs) should be used in the follow-up of the disease (4,8).

**References**

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