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Review Article

Refractory Hypoglycaemia Due to Insulin Autoimmune Syndrome: A Review of Published Cases

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Abstract

Background: Insulin autoimmune syndrome (IAS), or Hirata disease, is a rare cause of spontaneous, often postprandial, hyperinsulinaemic hypoglycaemia driven by high-titre autoantibodies against endogenous insulin, arising without prior exogenous insulin exposure.

Objective: To review published cases and epidemiological/mechanistic literature on IAS, focusing on drug-induced and idiopathic presentations and management of refractory disease.

Methods: Narrative review of individually verified case reports, case series, systematic reviews and diagnostic/management literature.

Findings: IAS is disproportionately reported in Japan and linked to HLA-DRB1*0406, but is increasingly recognised worldwide following sulfhydryl-group drugs (methimazole, alpha-lipoic acid) and clopidogrel. Diagnosis rests on markedly elevated total insulin with disproportionate C-peptide, insulin autoantibody positivity, and PEG precipitation to distinguish IAS from insulinoma or factitious hypoglycaemia. Most cases remit after dietary modification and trigger withdrawal within months; refractory disease has responded to corticosteroids, rituximab and immunoadsorption.

Conclusions: IAS should be considered early in unexplained hyperinsulinaemic hypoglycaemia to avoid unnecessary insulinoma work-up, reserving immunosuppression for genuinely refractory disease.

Keywords: Insulin autoimmune syndrome; Hirata disease; Hypoglycaemia; Insulin autoantibodies; Autoimmune hypoglycaemia

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Introduction

Insulin autoimmune syndrome (IAS), first described by Hirata in Japan in 1970, is one of two recognised forms of autoimmune hypoglycaemia and is characterised by spontaneous hypoglycaemic episodes, markedly elevated immunoreactive insulin, and high-titre autoantibodies to native insulin in patients with no history of exogenous insulin administration [1,2]. Unlike insulinoma, in which hypoglycaemia reflects unregulated endogenous insulin secretion, IAS reflects unpredictable release of insulin sequestered on autoantibody complexes, producing a pattern of hypoglycaemia that is often postprandial or nocturnal and can be severe enough to cause seizures or coma [3]. Historically a curiosity of Japanese case series, IAS is now increasingly reported in Western populations, frequently in association with sulfhydryl-group-containing drugs, and represents an important, correctable cause of otherwise unexplained hyperinsulinaemic hypoglycaemia [4,5]. Because its biochemistry can superficially resemble insulinoma or, if unrecognised, prompt costly imaging and even unnecessary pancreatic surgery, timely recognition of IAS carries direct clinical and economic importance [3]. This narrative review surveys published individual case reports, case series and epidemiological, mechanistic, diagnostic and management literature on IAS, drawing on drug-induced and idiopathic cases to characterise the modern published-case spectrum, including approaches to refractory, treatment-resistant disease — the clinical scenario most likely to prompt specialist referral and the focus of this review's title.

Epidemiology

IAS is the third leading cause of spontaneous hypoglycaemia in Japan, where by the mid-1990s nearly 200 cases had been reported, with clear female predominance in the 20-49-year age group [6]. This geographic clustering reflects a strong genetic association: IAS in Japan is almost invariably linked to HLA-DRB1*0406*, *an allele far more prevalent in Japanese, Korean and northern Chinese populations than in Europeans, explaining both the high incidence in East Asia and its comparative rarity elsewhere [7,8]. Outside Japan, IAS is increasingly recognised but remains rare and often drug-related; over 380 cases have now been reported*

*worldwide, with fewer than 70 in Western countries specifically, and the HLA linkage is less consistently replicated in non-Asian and alpha-lipoic acid-induced cases [3,8]. More than half of reported patients have a history of exposure to a sulfhydryl-group medication, most classically methimazole or carbimazole used for Graves' disease, but also captopril, hydralazine, isoniazid, imipenem and, increasingly, alpha-lipoic acid and clopidogrel [4,9,10]. IAS is also associated with other autoimmune and haematological conditions, including Graves' disease itself, systemic lupus erythematosus, and multiple myeloma [3]. Within Graves' disease specifically, essentially all Japanese patients who developed methimazole-associated IAS carried HLA-DRB1*0406*, whereas patients with Graves' disease who did not develop IAS did not, indicating that the allele is necessary though not sufficient and that drug exposure and genetic susceptibility act in combination rather than independently [7,11]. The apparent rarity of IAS outside East Asia therefore likely reflects both lower background HLA-DRB1*0406 prevalence and under-recognition, rather than a true absence of the biological predisposition, a point reinforced by the growing Western case literature identified for this review [3,12].

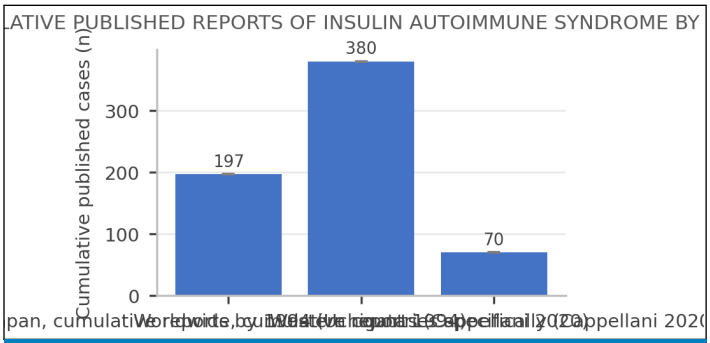

Figure 1: Cumulative published case burden of insulin autoimmune syndrome: 197 cases in Japan by 1994 [6]; over 380 worldwide and fewer than 70 in Western countries specifically by 2020 [3].

Pathophysiology

IAS arises when interaction between reactive drug metabolites (or, in idiopathic cases, an unidentified trigger) and the disulfide bonds of the insulin molecule renders endogenous insulin immunogenic, in a genetically susceptible host expressing permissive HLA class II alleles that present the modified insulin epitope efficiently to T cells [10,9]. The resulting polyclonal, high-capacity but low-affinity autoantibodies bind large quantities of secreted insulin postprandially, blunting the expected glucose-lowering effect and provoking compensatory hyperglycaemia and further insulin secretion. As glucose falls between meals, insulin dissociates unpredictably from the autoantibody pool, releasing a bolus of free insulin into the circulation independent of ambient glucose and precipitating delayed, often severe hypoglycaemia [3,2]. This buffering-and-release mechanism, rather than autonomous oversecretion as in insulinoma, is the pathophysiological core of the syndrome and explains both its characteristically postprandial-to-fasting timing and its tendency towards spontaneous remission once autoantibody titres decline after removal of the inciting trigger [2]. Antibody characteristics also matter clinically: IAS antibodies are typically polyclonal, with high binding capacity but low affinity, permitting the large buffered-insulin pool and its unpredictable release; this contrasts with the rarer monoclonal insulin autoantibody phenotype and with type B insulin resistance syndrome, in which autoantibodies target the insulin receptor itself rather than insulin, producing severe insulin resistance and hyperglycaemia rather than hypoglycaemia as the dominant early feature [2,13].

Clinical Presentation

Published cases span idiopathic and multiple drug-associated aetiologies. Alpha-lipoic acid, a dithiol-containing antioxidant supplement, has repeatedly triggered IAS, including a Caucasian woman with recurrent hypoglycaemia successfully managed with drug withdrawal and diazoxide [14], and a 40-year-old non-diabetic woman who presented unresponsive from

severe hypoglycaemia with markedly elevated fasting insulin, elevated C-peptide and positive anti-insulin antibodies, requiring corticosteroids after supplement withdrawal [15]. Methimazole-associated IAS, the originally described drug trigger, has been reported in a Korean adolescent girl treated for Graves' disease [11] and remains disproportionately represented in Japanese and Korean series [6]. Clopidogrel has emerged as a distinctive and increasingly recognised trigger, illustrated by an elderly White man with recurrent severe hypoglycaemia and markedly elevated insulin and C-peptide [16], a Chinese man with similar biochemistry [17], and further individually reported cases [18,19], now the subject of a dedicated systematic case review [20]. Idiopathic cases without an identifiable drug trigger are also well documented, including a report in an "occidental" (non-Asian) woman [12] and a three-patient case series [21], underscoring that IAS is not confined to drug exposure or East Asian ancestry.

Table 1: Published cases of insulin autoimmune syndrome reviewed here [14,15,11,16,17,18,19,12,21,24,26,25]; N = 12 reports.

Report	Age/sex	Suspected trigger	Presentation	Treatment	Outcome
Bresciani 2011	Not stated / F	Alpha-lipoic acid	Recurrent hypoglycaemia	Drug withdrawal, diazoxide	Resolved
Baburaj 2024	40 / F	Alpha-lipoic acid	Unresponsive, severe hypoglycaemia	Dextrose, corticosteroids	Resolved
Lee 2013	Not stated / F	Methimazole (Graves')	Hypoglycaemic episodes	Not stated	Not stated
Rajpal 2017	79 / M	Clopidogrel	Recurrent severe hypoglycaemia	Not stated	Not stated
Jiang 2020	63 / M	Clopidogrel	Hypoglycaemic episodes	Not stated	Not stated
Calder 2020; Yamada 2016	Not stated	Clopidogrel	Autoimmune hypoglycaemia	Not stated	Not stated
Reis 2018	Not stated / F	Idiopathic	Recurrent fasting hypoglycaemia	Not stated	Not stated
Chen 2018, n=3	Not stated	Not stated	Not stated	Not stated	Not stated
Church 2017	Not stated	Not stated, refractory	Hypoglycaemia + cardiovascular dysfunction	Rituximab	Resolved
Kroemer 2018	Not stated	Not stated, refractory	Refractory hypoglycaemia	Immunoadsorption + rituximab	Resolved
Batra 2021	Not stated	Not stated, steroid-refractory	Hypoglycaemia despite 1 month steroids	Rituximab + CGM	Controlled

Across the published case literature, the presenting pattern is consistent even where drug triggers differ: recurrent, often severe hypoglycaemia — occasionally to the point of unresponsiveness or coma, as in the alpha-lipoic acid case reported by Baburaj and colleagues [15] — typically emerging days to weeks after starting the culprit medication, in patients with no history of diabetes or exogenous insulin use. Symptoms range from adrenergic warning signs (sweating, tremor, palpitations) to neuroglycopenia, and the temporal relationship to meals is variable, distinguishing the overall pattern from the purely fasting hypoglycaemia more typical of insulinoma [5]. Extremely high measured total insulin, often disproportionate to the degree of hypoglycaemia and reported in some cases at values many-fold above the assay's normal range, is a recurring biochemical hallmark across these reports and is what most often first raises suspicion of IAS over insulinoma [16,17].

Diagnostic Approach

IAS should enter the differential whenever Whipple's triad-confirmed hypoglycaemia coexists with disproportionately or extremely elevated total serum insulin, since standard immunoassays measure both free and antibody-bound insulin [22,3]. Unlike insulinoma, in which insulin and C-peptide rise concordantly but modestly, IAS typically shows extremely high total insulin (often >100-1000 μU/mL) alongside proportionately elevated C-peptide and proinsulin, reflecting endogenous co-secretion rather than exogenous insulin

administration (which would suppress C-peptide) [5,10]. Insulin autoantibody assay confirms the diagnosis, but polyethylene glycol (PEG) precipitation of serum, followed by insulin measurement in the supernatant, is a key discriminating step: recovery of free insulin after PEG precipitation is markedly reduced in IAS because most immunoreactive insulin is antibody-bound, whereas recovery is preserved in insulinoma and factitious hypoglycaemia [23,3]. Gel filtration chromatography with ex vivo insulin exchange can further characterise antibody-binding capacity where PEG results are equivocal [23]. Cross-sectional imaging for insulinoma and screening for sulfonylurea or exogenous insulin use (factitious hypoglycaemia) should proceed in parallel or be deferred once IAS biochemistry is characteristic, since imaging is unnecessary and potentially misleading once the diagnosis is secure [22,20].

Table 2: Distinguishing insulin autoimmune syndrome from its principal differential diagnoses [22,23,5,3].

Feature	IAS	Insulinoma	Factitious/exogenous insulin
Total serum insulin	Markedly elevated, often extreme	Mildly-moderately elevated	Elevated (insulin) or variable
C-peptide	Elevated, proportionate	Elevated, proportionate	Suppressed if exogenous insulin
PEG-precipitable insulin recovery	Markedly reduced	Normal/preserved	Normal/preserved
Insulin autoantibodies	Positive, high titre	Negative	Negative (unless antibodies to exogenous insulin)
Typical trigger	Sulfhydryl drug or idiopathic	None (tumour)	Access to insulin/sulfonylurea

A careful medication history is itself a diagnostic step, given how frequently a sulfhydryl-group drug or supplement — antithyroid medication, alpha-lipoic acid, or clopidogrel — precedes onset by days to a few weeks [10,20]. Because insulinoma and factitious or surreptitious insulin/sulfonylurea administration are the principal alternative diagnoses in this clinical picture, and each carries different management implications (surgery for insulinoma; psychiatric evaluation for factitious disease; simple drug withdrawal for IAS), an efficient work-up that leads with total insulin, C-peptide, proinsulin and insulin autoantibody testing, followed by PEG precipitation where results are ambiguous, avoids the diagnostic odyssey — including unnecessary cross-sectional imaging and, in some historical reports, unwarranted pancreatic surgery — documented in a number of the published cases before IAS was eventually recognised [5,3].

Management, Including Refractory Cases

First-line management is dietary: frequent, small, low-glycaemic-index meals to blunt the postprandial insulin-antibody binding surge and avoid precipitous late dissociation-related hypoglycaemia [3]. Any implicated drug should be withdrawn immediately once identified, as in the alpha-lipoic acid and clopidogrel cases above [14,15,16]. Most patients, particularly drug-induced cases, remit spontaneously within three to six months as autoantibody titres decline, and roughly 80% of cases resolve without further intervention [3]. For persistent symptomatic hypoglycaemia, corticosteroids are the established second-line therapy, reducing autoantibody titres and hypoglycaemic frequency, as used in the Baburaj case after alpha-lipoic acid withdrawal alone proved insufficient [15]. Diazoxide has also been used adjunctively to blunt endogenous insulin secretion, as in an alpha-lipoic acid-induced case unresponsive to trigger withdrawal alone [14]. For truly refractory disease unresponsive to corticosteroids, the anti-CD20 monoclonal antibody rituximab has been used successfully, including a case in which rituximab produced resolution of both hypoglycaemia and an associated cardiovascular dysfunction [24], a steroid-refractory case managed with rituximab alongside continuous glucose monitoring [25], and a case treated definitively with immunoadsorption followed by rituximab [26]. Plasmapheresis and immunoadsorption more broadly have been used as rescue therapy to physically remove circulating autoantibody in severe or

refractory presentations, though such approaches remain reported only in isolated cases rather than validated by trial evidence [26,3]. Continuous glucose monitoring has been increasingly incorporated alongside pharmacological therapy in refractory cases, both to characterise the pattern of glycaemic excursions and to guide safe tapering of corticosteroids or rituximab as remission is established [25]. No randomised trial evidence exists to guide the choice or sequencing of second-line agents; management of refractory IAS therefore remains guided by accumulated case experience, extrapolation from rituximab's use in other insulin- and receptor-autoantibody-mediated disorders such as type B insulin resistance syndrome, and individualised specialist judgement [13,26].

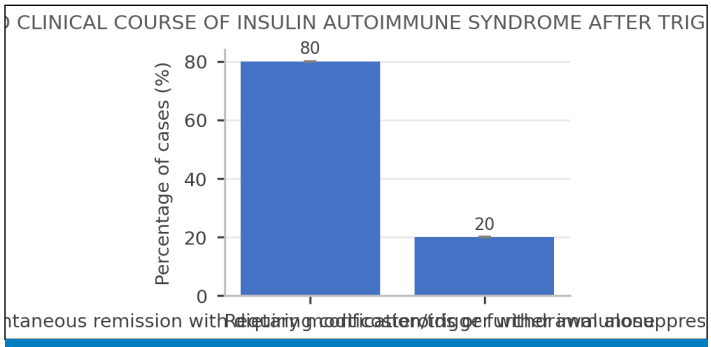

Figure 2: Reported clinical course after trigger identification and withdrawal: approximately 80% of published cases remit spontaneously within three to six months, with the remainder requiring corticosteroids or further immunosuppression [3].

Outcomes and Prognosis

The overall prognosis of IAS is favourable: the great majority of published cases, drug-induced and idiopathic alike, achieve durable remission with conservative management and trigger avoidance, without recurrence once autoantibody titres normalise [3,2]. Recurrence is uncommon but has been described on re-exposure to the same or a cross-reactive sulfhydryl-group agent, reinforcing the importance of documenting and avoiding the causative drug where one is identified [10]. Refractory or relapsing disease requiring escalation to rituximab or immunoadsorption appears rare in the published literature but can be effectively controlled, with reported cases achieving sustained resolution of hypoglycaemia [24,26,25]. No published case series report IAS-related mortality directly attributable to the autoimmune process itself, though morbidity from unrecognised or delayed diagnosis—including unnecessary pancreatic imaging, and risk from severe unrecognised hypoglycaemia—remains the principal published concern [5,20].

Conclusion

Insulin autoimmune syndrome is an uncommon but likely under-recognised cause of hyperinsulinaemic hypoglycaemia, historically concentrated in Japan through HLA-DRB1*0406 but increasingly reported worldwide, particularly with sulfhydryl-group drugs including methimazole, alpha-lipoic acid and clopidogrel. Recognising the characteristic biochemical pattern—markedly elevated total insulin with disproportionate C-peptide and reduced PEG-precipitable insulin—allows prompt diagnosis and avoidance of unnecessary insulinoma work-up. Most cases resolve with dietary modification and trigger withdrawal alone; corticosteroids, rituximab and immunoadsorption offer effective options for the minority with refractory disease.

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