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REVIEW

Insulin Autoimmune Syndrome (Hirata Disease): A Comprehensive Review Fifty Years After Its First Description

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Abstract: Insulin autoimmune syndrome (IAS), also named Hirata's disease, is a rare condition characterized by hypoglycemic episodes due to the presence of high titers of insulin autoantibodies (IAA). IAS is a form of immune-mediated hypoglycemia, which develops when a triggering factor (ie, a medication or a viral infection) acts on an underlying predisposing genetic background. IAS pathogenesis involves the formation of insulin-IAA complexes that induce glycemic alterations with a double-phase mechanism: IAA prevent insulin to bind its receptor in the postprandial phase, possibly resulting in mild hyperglycemia; thereafter, insulin is released from the complexes irrespective of blood glucose concentrations, thus inducing hypoglycemia. The diagnosis of IAS is challenging, requiring a careful workup aimed at excluding other causes of hyperinsulinemic hypoglycemia. The gold standard for the definitive diagnosis is the finding of IAA in a blood sample. Because IAS is frequently a self-remitting disease, its management mostly consists of supportive measures, such as dietary modifications, aimed at preventing the development of hypoglycemia. Pharmacological therapies may occasionally be necessary for patients presenting with severe manifestations of IAS. Available therapies may include drugs that reduce pancreatic insulin secretion (somatostatin analogues and diazoxide, for instance) and immunosuppressive agents (glucocorticoids, azathioprine and rituximab). The purpose of this review is to provide a comprehensive analysis of the disease, by describing the burden of knowledge that has been obtained in the 50 years following its first description, took in 1970, and by highlighting the points that are still unclear in its pathogenesis and management.

Keywords: insulin autoimmune syndrome, IAS, Hirata, hypoglycemia, autoimmunity

Introduction

Insulin autoimmune syndrome (IAS) is a rare condition, characterized by spontaneous episodes of hyperinsulinemic hypoglycemia due to the presence of high serum concentrations of insulin autoantibodies (IAA). IAS is also named Hirata's disease, after the original description made in 1970 by Yukimasa Hirata and colleagues.[1] IAS is one of the two types of autoimmune hypoglycemia, being the other type B insulin resistance, which is due to antibodies against the insulin receptor.[2–4] According to its original definition, IAS develops in individuals who were not previously exposed to exogenous insulin and who do not present pathological abnormalities of the pancreatic islets; nevertheless, cases of glycemic instability were more recently reported in insulin-treated patients as a consequence of the development of insulin antibodies with biochemical and clinical features that were similar to those of IAA.[5] The pathogenesis of IAS has been extensively investigated and the mechanisms

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underpinning the glycemic fluctuations described in IAS have been identified in a mismatch between plasma glucose and insulin concentrations, due to the presence of IAA. The diagnostic workup of IAS is complex and aims at a correct and complete differential diagnosis with other forms of hypoglycemic disorders.[6] Despite being a condition that often undergoes self-remission, IAS management remains challenging, given the absence of committed specific therapies and the lack of comparison between the different therapeutic regimens that have been proposed. For the purposes of the present review, we performed a computer-aided literature search of the MEDLINE database; moreover, we examined the reference lists of the published articles, case reports and reviews. Studies that were published in languages other than English were excluded. The database was searched for articles published until September 2019.

Historic Perspectives

IAS was originally described in 1970 by Yukimasa Hirata and colleagues in a 47-year-old obese male with recurrent severe hypoglycemic episodes.[1] For several years after the original Hirata's description the reports of this condition were scanty and mostly, but not exclusively, from Japan.[7–10] A subsequent milestone in the history of IAS includes the identification of the association with the exposure to sulphydryl medications in 1983.[11] Many steps forward in the identification of the pathogenesis of IAS were taken during the 1990s: for instance, the association with specific immunogenic determinants was described in 1992,[12] whereas the IAS was identified as a form of type VII hypersensitivity in 1995.[13] In the last 20 years, many additional cases of IAS have been reported worldwide, deepening our knowledge on its pathogenesis and providing new tools for the diagnostic and therapeutic approaches to this disease.

Epidemiology

The exact incidence of IAS is still a matter of debate, being probably underestimated due to the difficulties in the diagnostic workup, the self-limiting nature of the disease, and the general unawareness of this disease until the last decade. A brief summary of the main epidemiological studies on IAS is reported in Table 1. Three hundred eighty cases of IAS were reported worldwide from 1970 to 2009.[14] According to our knowledge, there is no published study

Table 1 Main Epidemiological Studies on Insulin Autoimmune Syndrome (IAS)

Authors	Year	Study Population	Estimated Incidence/Prevalence of IAS	Ethnicity of the Study Population	Reference
Takayama-Hasumi et al	1990	Patients admitted to 2094 Japanese hospitals for hypoglycemic episodes	Prevalence: 11.7% of a selected cohort (41 cases over 350 patients)	Japanese	[16]
Uchigata et al	1994	Reports of IAS published/presented in Japan from 1970 to 1992	Incidence: 9 cases per year (197 cases over 22 years)	Japanese	[22]
Uchigata et al	2000	Review of the published cases from 1970 to 1997	Incidence: 9 cases per year (244 cases over 27 years)	Japanese	[20]
			Incidence: 1 case per year (26 cases over 27 years)	Caucasian	
Uchigata et al	2009	Review of the published cases from 1970 to 2007	Incidence: 10.3 cases per year (380 cases over 37 years)	Worldwide	[14]
Woo et al	2015	Patients hospitalized for hyperinsulinemic hypoglycemia	Prevalence: 6% of a selected cohort (5 cases over 84 patients)	Korean	[18]
Wang et al	2015	Patients identified by a nationwide questionnaire survey on IAS	Incidence: 2.6 cases per year (73 cases over 28 years)	Chinese	[19]
Yamada et al	2019	Patients identified by a nationwide survey on endogenous hyperinsulinemic hypoglycemia	Prevalence: 4.9% of a selected cohort (22 cases over 447 patients). Estimated prevalence in the general population: 0.017 cases per 100.000 population	Japanese	[17]

that reported the exact worldwide incidence of IAS after 2009. On one hand, this may be due to the fact that newly found cases of IAS lacking of clinical novelty may have been considered unsuitable for publication by many Journals;[15] on the other hand, many large retrospective cohort studies include patients that had already been described in single case reports or smaller series, thus making difficult the identification of the real incidence of the disease.

IAS was originally described in Japan, and in 2009 over 90% of the published cases were reported in the Japanese population, where this disease was considered the third most common cause of hypoglycemia, after insulinoma and extrapancreatic neoplasias.[15,16] The most recent study estimating the epidemiology of IAS in the Japanese population was conducted in 2019, and it reports an estimated prevalence of 0.017 cases per 100.000 in the general population.[17] The prevalence of IAS in Korea was retrospectively estimated to be the 6% of a cohort of 84 patients undergoing a diagnostic workup for endogenous hyperinsulinemic hypoglycemia at a referral hospital.[18] The prevalence of IAS in China was reported to be much lower, accounting for only 73 cases over a 30-years span.[19] Although the first report of IAS in a Caucasian patient was published early in 1972,[8] the disease has always been considered quite rare outside Asia. Yet, an increasing number of cases have been reported in the last decades in Caucasians.[3]

The uneven geographic distribution of IAS was primarily attributed to the evolutionary distribution of the HLA system alleles.[20] However, this theory is counterbalanced by the observation that in more recent years the incidence of this disease has been increasing more evenly worldwide. Whether the reason for this epidemiological trend should be identified in the wider usage of medications and supplements that have been associated to IAS,[4] or to the greater awareness for the disease and the wider availability of IAA assays is still a matter of debate.[4]

IAS seems to affect both sexes equally.[3,21] The peak age at onset was originally reported in the seventh decade.[22] However, it is nowadays known that the age at onset varies widely, and a temporal difference in its incidence among males and females was observed with an earlier incidence (fourth decade) for females and a later incidence (seventh decade) for males.[19] IAS is rare in the pediatric population, even though there are scattered reports in children.[23,24]

Classification

Insulin autoimmune syndrome can be classified taking into account different perspectives. First of all, IAS can be classified on the basis of a previous exposure to exogenous insulin, which would determine a subdivision between patients who were previously exposed and patients who were not. This classification seems pleonastic, since IAS was originally defined as a syndrome developing in patients who were not previously exposed to exogenous insulin, as reported above. Nevertheless, given the presence of manuscripts describing IAS in diabetic patients who were previously treated with insulin therapy,[25–27] we decided to include this introductory classification in order to provide a more complete overview of the disease.

Secondly, IAS can be classified according to the association with other autoimmune diseases: on the one hand, it can be a solitary manifestation of autoimmunity, whereas on the other hand it can be associated with other autoimmune diseases, being included in type 3A or in type 4 autoimmune polyendocrine syndrome.[28] The linkage between IAS and Graves' disease that was originally identified[9] has been subsequently clarified:[11,29] these two different autoimmune diseases may be associated not as independent manifestations of a common autoimmune condition, but because IAS may be the consequence of the exposure to antithyroid drugs administered to the patient for the cure of the hyperthyroidism. The association of IAS with other forms of autoimmunity was described more frequently in Caucasian than in Asian patients.[3]

Moreover, IAS can be classified by distinguishing between drug-induced forms and apparently-spontaneous ones.[14] The list of medications associated with IAS is long, and includes the medications reported below and summarized in Table 2. The prevalence of drug-induced forms was estimated to be 43% in a Japanese series of 197 IAS patients diagnosed from 1970 to 1991.[22] Similarly, in 2009 it was estimated that drug-induced IAS accounted for about the 50% of the total in the Caucasian population.[3] Given the progressive extension of the list of medications that have been associated to the development of the syndrome, more recent studies hypothesized that the above-mentioned estimates of drug-induced IAS were underestimating the problem, being the actual prevalence above eighty percent.[19]

Table 2 List of Medications Associated with the Development of Insulin Autoimmune Syndrome

Class	Medication	References	Strenght of the Association
Antithyroid drugs	Methimazole	[9,11,23,29,37–41]	High
	Carbimazole	[42–47]	Medium
Supplements	Alpha-lipoic acid	[33–35,48–52]	High
	Pyritinol	[53,54]	Low
	Glutathione	[21]	Low
	Methionine	[55]	Low
Antihypertensives	Captopril	[22,36]	Low
	Hydralazine	[56,57]	Low
	Procainamide	[56]	Low
	Diltiazem	[22]	Low
Antiplatelet drugs	Clopidogrel	[58,59]	Low
Oral antidiabetics	Tolbutamide	[22]	Low
	Gliclazide	[60]	Low
Anti-inflammatory drugs	Steroids	[22]	Low
	Loxoprofen-sodium	[61]	Low
	Diclofenac	[22]	Low
Muscle relaxants	Tolperisone hydrochloride	[22]	Low
Antibiotics	Penicillamine	[62,63]	Low
	Imipenem	[64]	Low
	Penicillin G	[65]	Low
	Isoniazid	[66]	Low
Proton pump inhibitors	Pantoprazole	[67]	Low
	Omeprazole	[68]	Low
Plasma proteins	Albumin	[69]	Low
Orphan drugs	Tiopronin (Mercaptopropionyl glycine)	[21,22]	Low

Notes: The strength of the association has been defined as low (less than 5 reports), medium (between 5 and 9 reports), or high (more than 10 reports).

Etiology

The etiopathogenesis of IAS has not been fully understood. The most widely accepted theory is that IAS results from the interaction of a genetic predisposition with environmental triggers, thus leading to the production of insulin autoantibodies which have a pathogenic role.[15]

The genetic background of the syndrome was extensively investigated from the early 1990s. The immunogenetic determinants for the IAS were identified in the genes of the class II Human Leukocyte Antigen (HLA) system: the disease resulted strongly associated with HLA-DR4 and specifically with the DRB1*0406 and, although less significantly, DRB1*0403 and DRB1*0407.[12,30,31] The higher prevalence of HLA-DRB1*0406 in Asian populations was advocated as the determinant of the higher incidence of IAS in Japan compared to the western countries.[20] Furthermore, a correlation between the genetic background and the risk of developing a particular form of drug-induced IAS (ie methimazole-induced IAS in patients with Graves' disease) was also postulated: the incidence of methimazole-induced IAS is particularly high in Japan compared to other countries, and the patients who develop IAS following methimazole exposure invariably carry the DRB1*0406 allele.[32] As a consequence, the lower incidence of methimazole-induced IAS outside Japan was supposed to be due to the lower prevalence of the HLA-DRB1*0406 in the general population.[20] HLA-DRB1*0406 was originally supposed to be also associated with the alpha-lipoic acid-induced IAS in Japanese patients,[33] but this finding was not confirmed nor in Caucasians,[34] nor in other Asian populations.[35] More recent papers describing case reports of IAS outside Asia did not uniformly confirm the linkage of the IAS with the above-mentioned immunodeterminants, suggesting that the genetic spectrum of the syndrome may be broader

(especially outside Asia), and thus indicating the need of further studies to understand more deeply the genetic background of the syndrome.[24,36]

Many different triggers have been advocated to induce the development of IAS when acting on an underlying predisposing background: among them, in order of importance, there are medications, viruses and hematological diseases.

The list of medications that have been suspected as possible triggers for the development of IAS is reported in Table 2.

This list has been progressively extended to include new medications, most of which have been added during the last ten years. However, many of the drugs that have been proposed as potential triggers for the development of IAS have been merely reported by one single paper. This point claims that more solid confirmatory evidences are required for most of the cited drugs. At present, methimazole[9,11,37,38] and alpha-lipoic acid[33–35,48] remain the only medications whose exposure has been more commonly linked to the development of IAS. It is noteworthy that the association between alpha-lipoic acid and IAS has been increasing during the last decade.[14] Alpha-lipoic acid is a compound that is widely prescribed in many medical fields, mainly due to its antioxidative properties:[70] as a consequence, it has been proposed as an adjuvant therapy for instance in diabetic neuropathy,[71,72] polycystic ovary syndrome,[73] central nervous system related diseases[74] and as a supplement for dieting and anti-aging.[14] To date, alpha-lipoic acid-induced IAS seems more common than methimazole-induced IAS.[34]

Importantly, the medications associated with IAS are mostly sulphydryl and reducing compounds, providing a clue regarding a possible pathogenesis of the disease. The proposed mechanism is that these drugs would bind and cleave the sulphydryl bonds between the insulin chains A and B, thus leading to a conformational change in its molecular structure that makes the endogenous insulin more immunogenic:[75] as a matter of fact, following the cleavage of the bonds between the insulin chains, the antigen-presenting cells may bind much more of the linear fragment of the insulin A chain, thus leading to the activation of self-directed insulin-specific T-helper cells.[76] However, IAS has also been reported in patients that were taking medications that do not contain sulphydryl bounds, such as albumin.[69] The onset timing of drug-induced IAS varies widely: as a matter of fact, while some authors report the onset of the first IAS manifestations few days after the first administration of the responsible medication,[35,49] others identify a longer onset time, up to many months.[34,37] The mean onset time was estimated to be four to six weeks following the beginning of the offending medication.[22] Yet, there are reports of drug-induced IAS developing years after the first administration of the offending medication, due to an additional and subsequent cycle of the medical therapy.[39]

Many viral infections have been reported to be triggers for the development of IAS: measles virus, mumps virus, rubella virus, varicella zoster virus, coxsackie B virus and hepatitis C virus.[77] The supposed mechanism is that the viral infection acts as a super-antigen, thus triggering the production of the IAA that cause the syndrome.[78]

The association with hematological disorders, such as multiple myeloma or monoclonal gammopathy of undetermined significance has been described in Caucasians.[79]

There are many reported cases of patients who develop IAS without a previous history of exposure to known triggering factors. This spontaneously-onset IAS has been mostly reported in Japan, whereas it seems a quite rare phenomenon in western countries. It has been proposed that the cases that were reported as spontaneously-onset were actually determined by triggers that underwent misrecognized.[19]

Pathogenesis

IAS has been described as a form of type VII hypersensitivity, characterized by the presence of autoantibodies against a circulating antigen.[13] The cornerstone of the IAS is the appearance of circulating insulin autoantibodies (IAA), which have a pathogenic role in the development of the syndrome, and play also a central diagnostic role in this disease. IAA are immunoglobulins (Ig) directed against the native endogenous insulin molecule. They may belong to different Ig classes, although they are more commonly IgG;[4] IAA belonging to IgA and IgM are definitely rare, although described.[77,80] Due to their high binding capacity, IAA are able of binding several molecules of insulin, resulting in the formation of large antigens-antibodies complexes. On the other hand, the low affinity for insulin is responsible for a significant spontaneous dissociation rate, which inappropriately raises unbound insulin concentrations, thus resulting in hypoglycemic episodes, as reported below. High binding capacity and low affinity are the specific features of the IAA that are capable of inducing IAS.[81] As a matter of fact, even though modern insulin analogs have a low immunogenicity, insulin antibodies may sometimes be detected in patients receiving insulin therapy, but these antibodies are rarely capable of causing hyperglycemia or

hypoglycemia.[25] This is because the insulin antibodies that develop following exposure to exogenous insulin are more often characterized by a higher affinity and a lower binding capacity against insulin compared to IAA. As a consequence, they mostly result in smaller antigen-antibody complexes which have a lower spontaneous dissociation rate, thus they are unable to produce significant glycemic fluctuations.[5] Nevertheless, insulin antibodies developing after the administration of exogenous insulin may seldom present with features similar to those of IAA, such as a high binding capacity and low affinity, thus resulting in glycemic instability.[5,82,83]

IAA have no pathological effects when present at small titers: up to 2% of a cohort of healthy blood donors presented small titers of IAA, without any previous or current manifestation of IAS.[84]

The presence of the IAA induces IAS with a double-phase mechanism, which is constantly underpinned by a mismatch between blood glucose concentrations and free insulin concentrations,[15,85] as reported in Figure 1. The first phase takes place when insulin normally secreted by the pancreatic beta-cells in response to rising plasma glucose concentrations binds to autoantibodies, becoming unable to exert its physiological effects. In other terms, in this first phase, insulin-IAA complexes hinder the physiological mechanisms of insulin action,[86] thus resulting in low unbound insulin concentrations and consequent transient hyperglycemia. Early postprandial hyperglycemia is a further stimulus for the secretion of insulin molecules that are partly bound to circulating insulin-IAA complexes and partly unbound and free to exert its physiological action. Spontaneous dissociation of insulin from the complexes does not cease when plasma glucose concentrations lower, thus resulting in a relative excess of unbound insulin, which evokes hypoglycemia.[15,86]

A few reports show the pathological examinations of IAS patients who underwent invasive procedures due to an initial mistake in differential diagnosis with insulinoma: the changes reported were consistent with pancreatic islets hyperplasia in one case[87] and nesidioblastosis in another case.[18]

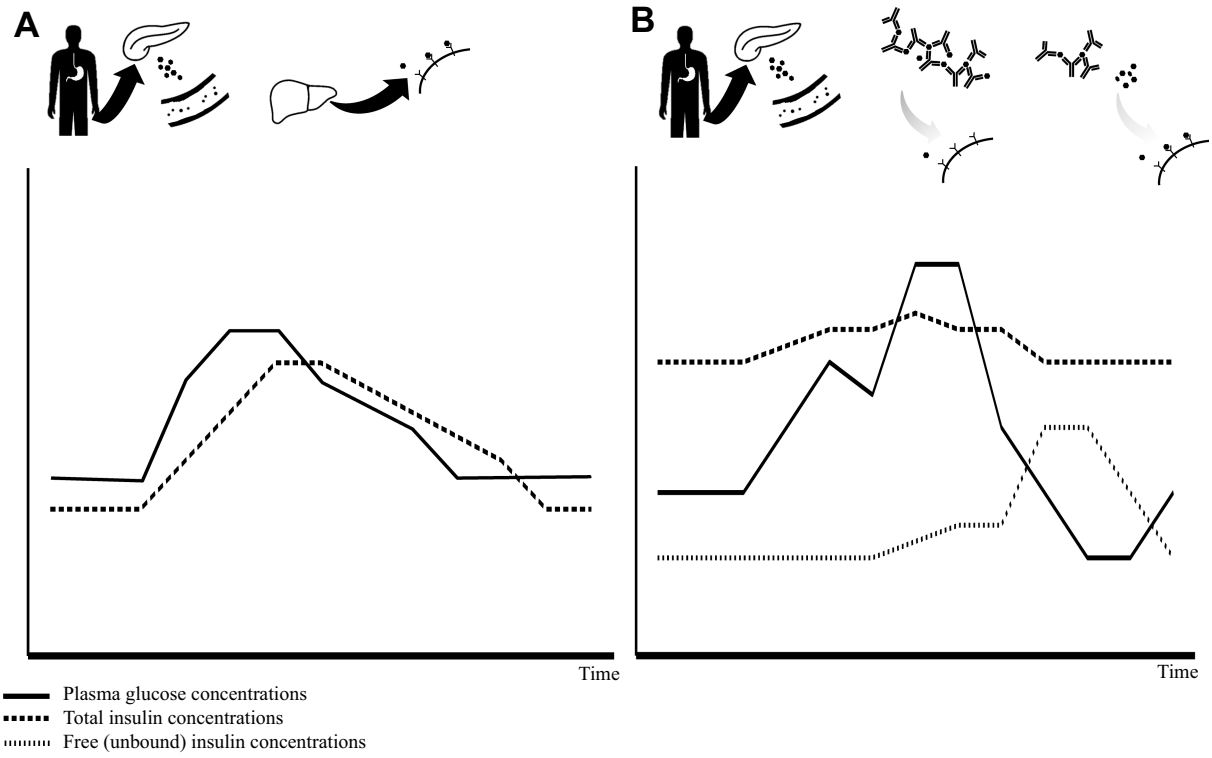

Figure 1 The insulin autoimmune syndrome pathogenesis.

Notes: Panel (**A**) schematic overview of the physiologic insulin secretion and action: following glucose intake, pancreatic beta-cells secrete insulin which enters into the bloodstream, getting to peripheral tissues when it exerts its physiological functions in order to maintain glucose homeostasis. Panel (**B**) schematic overview of the double-phase mechanism of the insulin autoimmune syndrome. Following glucose intake, pancreatic beta-cells secrete insulin which enters into the blood stream getting included in the insulin-IAA macro-complexes. In the early postprandial phase, inclusion intro macro-complexes prevents insulin to act on its receptors in peripheral tissues, thus inducing hyperglycemia (phase 1). Due to the relatively low affinity for insulin, IAA subsequently release insulin molecules irrespective of plasma glucose concentrations, thus inducing hypoglycemic episodes (phase 2). Below both panels is reported a schematic representation of glucose and insulin concentrations over time: the continuous line represents plasma glucose concentrations, dotted line represents total insulin, pointed line represents free unbound insulin.

Clinical Presentation

The clinical manifestations of IAS vary widely in terms of severity, duration and remission rates.[15] The clinical hallmark of IAS is hypoglycemia, which manifests with autonomic (hunger, seating, tremor, anxiety) and neuroglycopenic (irritability, behavioral changes, confusion, amnesia, seizures, loss of consciousness) symptoms.[88] Importantly, the cut-off to elicit hypoglycemic symptoms is much lower in patients who suffer from recurrent hypoglycemia compared to healthy patients.[89] IAS-induced hypoglycemia is usually mild, even though cases presenting with severe manifestations (up to seizures and coma) have been reported.[37,57,66,90]

An important point is the timing of hypoglycemia in relation to meals: most patients present postprandial hypoglycemia,[3] which is consistent with the pathogenic mechanism described above. However, there are reports of patients presenting with fasting hypoglycemia or even unpredictable hypoglycemic episodes.

In line with the supposed pathogenic mechanism[86] described above, patients may present with swings from hyperglycemia to hypoglycemia. In such circumstances, the typical presentation consists in early postprandial hyperglycemia and subsequent reactive hypoglycemia, as described in the earliest report of IAS in a Caucasian patient.[8] Glycated hemoglobin concentrations may vary according to the frequency and severity of hypoglycemic attacks and to the presence of glucose concentrations swings, so normal or even increased HbA1c concentrations can be found.[36,86] An increase in body weight has been reported, especially in patients presenting with long-lasting misrecognized IAS.[36] Whether this point could be due to the increased food intake as a corrective mechanism for hypoglycemia, or to the anabolic effects exerted by hyperinsulinemia, has not been investigated.

Finally, for patients presenting IAS as a manifestation of a wider autoimmune movement, hypoglycemia can be preceded, accompanied or followed by other autoimmune manifestations, involving other endocrine glands, or other organs and systems.[28]

Diagnosis

When approaching a patient affected by hypoglycemia, the differential diagnosis between the different possible causes is mandatory, although challenging.[6] As a matter of fact, the therapeutic approach to hypoglycemia is strictly dependent on its cause. Although rare, IAS should be suspected in any patient presenting with hypoglycemia, in order to avoid any unnecessary diagnostic and therapeutic procedure.[91] A flow-chart of the diagnostic work-up of IAS is shown in Figure 2.

The first step in the approach to IAS is confirming the diagnosis of hypoglycemia, which can be proved by the presence of the Whipple triad: symptoms or signs of hypoglycemia associated with low plasma glucose concentrations ($\leq$ 70 mg/dL),[92,93] and resolution of those symptoms or signs after the plasma glucose concentration is raised by glucose administration. The documentation of the hypoglycemic episode is mandatory, since the nature of the hypoglycemia-related symptoms is not pathognomonic. If hypoglycemia does not appear spontaneously it should be investigated, even with the use of a fasting evaluation (up to 72 hours fast) with repeated measures of plasma glucose concentrations.[6] The oral glucose tolerance test is not routinely suggested in the work-up of the patient presenting for hypoglycemia.[6] In the specific case of IAS, the individual responses to the oral glucose administration show a wide variability,[94] and different glycemic responses to the oral glucose load were identified in the same patient when tested at different IAA titers.[95]

The second step consists in assaying serum insulin concentrations during a hypoglycemic episode.

Usually patients affected by insulin autoimmune syndrome present with extremely high insulin concentrations, often above 1000 pmol/L,[42] which is a rare finding in other forms of hyperinsulinemic hypoglycemia.[85] Interestingly, insulin concentrations can vary widely when assayed with different kits. The immunoradiometric assay (IRMA) is far more accurate for the dosage of unbound insulin compared to immunochemiluminometric assays (ICMA).[35] Hypoglycemia factitia due to exogenous insulin administration is another possible cause of hyperinsulinemic hypoglycemia. Because different insulin assays may exhibit variable cross-reactivity with insulin analogues,[96] it is not possible to differentiate hypoglycemia factitia from IAS by these insulin assays. However, once hyperinsulinemic hypoglycemia has been confirmed, C-peptide and proinsulin are useful for differentiating between endogenous and exogenous forms of hyperinsulinemia.[6] Low C-peptide and proinsulin are suspicious for exogenous insulin administration. On the contrary, high or inappropriately normal C-peptide and proinsulin concentrations are found in endogenous hyperinsulinemia, such as insulinoma or IAS.

A possible caveat of relying on C-peptide and proinsulin testing is that they do not allow the exclusion of other forms of hypoglycemia factitia, such as those due to oral

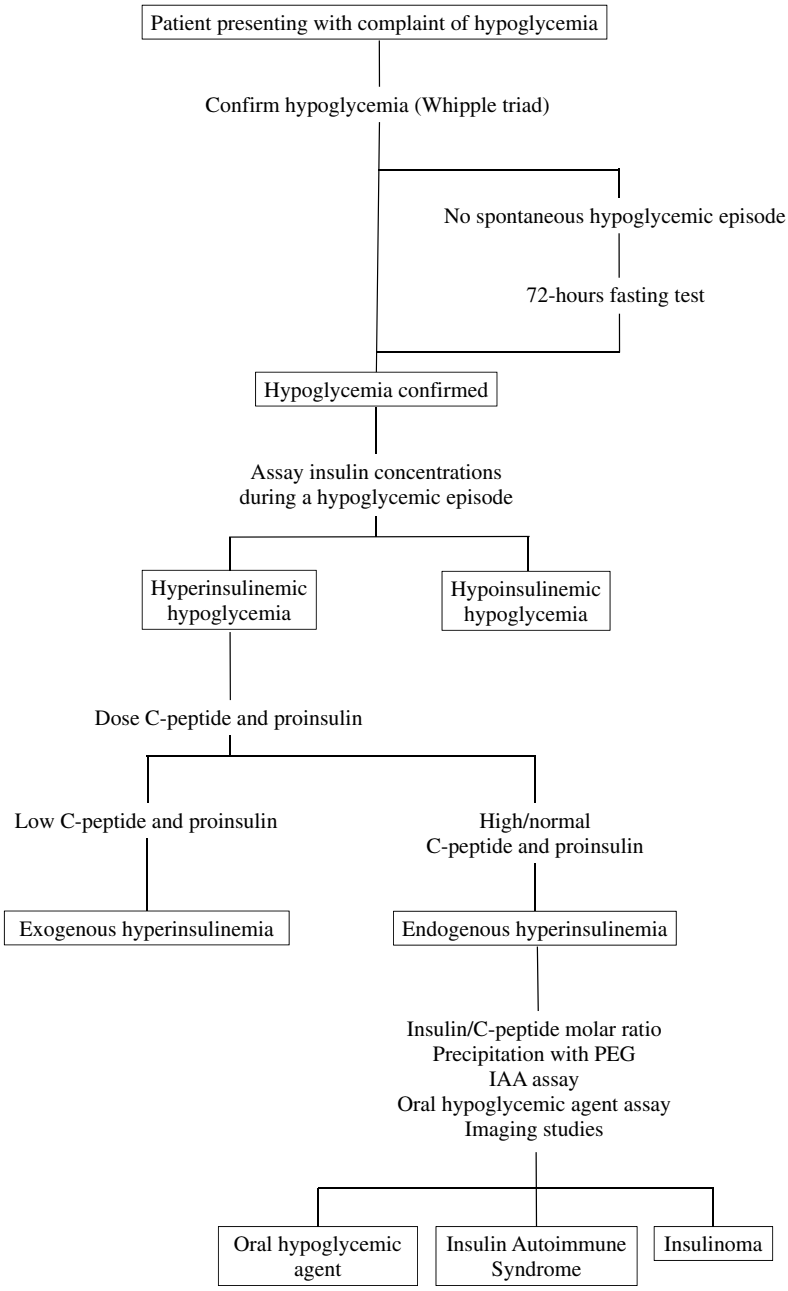

Figure 2 Flowchart for the diagnosis of insulin autoimmune syndrome.
Abbreviations: PEG, polyethylene glycol; IAA, insulin autoantibodies.

hypoglycemic agents, such as sulfonylureas. The administration of these drugs can be excluded by dosing their presence in a blood sample.[97]

Insulin to C-peptide molar ratio has been proposed as a diagnostic tool for IAS.[98] Pancreatic beta-cells secrete insulin and C-peptide in equimolar proportions, however these molecules have different half-lives, being 5–10 mins for insulin and 30–35 mins for C-peptide. As a consequence, the physiologic insulin to C-peptide molar ratio is lower than 1. The insulin to C-peptide molar ratio may be theoretically reversed to higher than 1 in IAS (due to the substantially higher insulin concentrations as a consequence of the prolonged half-live on the insulin molecules that are bound in the insulin-IAA complexes) and in exogenous insulin administration (due to the hypoglycemia-driven suppression of endogenous insulin secretion, which is responsible for the lower C-peptide concentrations).[91,98] However, the use of insulin to C-peptide molar ratio in the diagnosis of IAS

has been strongly criticized, given that C-peptide and proinsulin concentrations may vary widely in this condition, depending on the IAA capacity of binding these molecules as well, or to their ability to interfere with the available immunoassays.[4]

Precipitation with polyethylene glycol (PEG), followed by insulin assay in the supernatant has been proposed as a method for detecting the IAA.[34] The recovery of insulin following PEG precipitation results substantially lower in the sera of patients affected by IAS compared to healthy controls. However, proven that gel filtration chromatography with the addition of exogenous insulin may enhance the sensitivity for the identification of insulin immunocomplexes,[78] precipitation with PEG should be used cautiously when searching insulin-IAA complexes.[36]

The measurement of IAA titer is mandatory for the diagnosis of IAS[99] since it is the only lab test that allows a reliable diagnosis of IAS.[4] However, the availability of IAA assay is not widespread and the results of this test are obtained with delay, therefore preliminary confirmatory tests are performed. A possible pitfall in the measurement of IAA is that most of commercially-available assays are able to identify only IgG class of IAA, thus producing false negative results in the rare patients who present other classes of IAA.[4] In this context, the PEG precipitation can be considered a preliminary test, given its ability to precipitate IAA of any class.

Antibodies directed towards insulin may be detected in insulin-treated patients and even in healthy donors.[84] In this context, a Scatchard analysis[100] may be used with the aim to characterize the antibodies' features, such as their affinity for the antigen and their binding capacity.[81,101] The typical antibodies detected in the IAS present high binding capacity and low affinity for the endogenous insulin molecule.[5,101]

Imaging studies are obviously useless in the diagnosis of IAS. However, given the difficulties in the differential diagnosis with other forms of endogenous hyperinsulinemic hypoglycemia, IAS patients often undergo inappropriate and expensive imaging studies in their diagnostic workup. The incidental finding of a lesion at imaging studies may induce the execution of further examinations or even invasive procedures.

It is still a matter of debate whether a thorough screening aimed at excluding any associated autoimmune disease in the context of a PGA may be cost-effective, once the diagnosis of IAS is made.

A scheme for the differential diagnosis with other forms of hypoglycemia is reported in Table 3. Briefly, due to its higher prevalence[102] and the underlying similarities, insulinoma is the disease that enters more often in differential diagnosis with IAS. As a matter of fact, insulinoma is another form of endogenous hyperinsulinemic hypoglycemia, just like IAS. However, IAS-induced hypoglycemia is more often milder compared to insulinoma and, on the contrary, IAS-induced hyperinsulinemia is much higher compared to insulinoma.[42,85] Given the possibility that insulinomas may not be detected at conventional imaging studies,[103,104] the only reliable tool for the differential diagnosis is the assay for IAA, that are present in IAS but absent in insulinomas. Nesidioblastosis may result in the noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), another cause of endogenous hyperinsulinemic hypoglycemia that appears more often after a meal.[105,106] This condition is much rarer than insulinoma. Furthermore, the development of NIPHS may be preceded by a history of gastric surgery and dumping syndrome.[107,108] The presence of the latter points in the patient's past clinical history may be useful in the diagnostic work-up, even though the ultimate tools used for differentiating nesidioblastosis from IAS are the same available for the differential diagnosis with insulinoma.[6] The results of a recent Korean study prove that the differential diagnosis between IAS and other forms of endogenous hyperinsulinemic hypoglycemia is impossible without the availability of the IAA assay: the incidence of nesidioblastosis at a tertiary-level hospital declined after IAA assays were introduced as a routine test for patients presenting for hyperinsulinemic hypoglycemia.[18] Hypoglycemia due to exogenous insulin administration (in the set of psychiatric conditions or surreptitious usage) is a form of hyperinsulinemic hypoglycemia associated with low C-peptide and proinsulin concentrations[97,109] and, obviously, not associated with IAA.[110] More complex is the differential diagnosis with other forms of drug-induced hypoglycemia, such as those due to the administration of oral hypoglycemic agents: the definitive diagnosis of sulfonylurea-induced hypoglycemia can be obtained by assaying for the presence of these medications in a blood sample.[6] Type B insulin resistance is another form of autoimmune hypoglycemia,[3] which is due to the presence of autoantibodies which bind to the insulin receptor exerting agonistic effects, thus resulting in insulin resistance and paradoxical hypoglycemia.[4] Patients affected by type B insulin resistance often display features of severe insulin resistance, such as severe diabetes mellitus poorly responsive to insulin therapy and acanthosis nigricans,[111] which are usually not present in patients affected by IAS. Despite this

Table 3 Diagnostic Tools for the Differential Diagnosis Between Hypoglycemias of Different Origins

	Insulin	C-Peptide	Proinsulin	Insulin/ C-Peptide Molar Ratio	Presence of Oral Hypoglycemic Agent in a Blood Sample	Insulin Recovery Following Precipitation with PEG	Antibodies Assays	Imaging Studies
Insulinoma	↑	↑/inappropriately normal	↑/inappropriately normal	< 1	Negative	Normal (> 70%)	Antibody- negative	May be positive
Nesidioblastosis	↑	↑/inappropriately normal	↑/inappropriately normal	< 1	Negative	Normal (> 70%)	Antibody- negative	Generally negative
Exogenous insulin administration	↑	↓	↓	> 1	Negative	Normal (> 70%)	Antibody- negative	Generally negative
Oral hypoglycemic agents administration	↑	↑/ inappropriately normal	↑/ inappropriately normal	< 1	Positive	Normal (> 70%)	Antibody- negative	Generally negative
Type B insulin resistance	↑↑/↑	↑↑/↑/ inappropriately normal	↑↑/↑/ inappropriately normal	< 1	Negative	Normal (> 70%)	Antireceptor insulin antibodies	Generally negative
Insulin autoimmune syndrome	↑↑/↑ (depending on the insulin assay)	↑↑/↑ (depending on IAA affinity for the C-peptide)	↑↑/↑ (depending on IAA affinity for the C-peptide)	Generally > 1	Negative	Low (5-10%)	IAA (false negative if IAA different from IgG with some laboratory kits)	Generally negative

Notes: ↑ indicates an increase, whereas ↓ indicates a decrease. The magnitude of the increase/decrease is indicated by the number of arrows.

clinical difference, the only reliable method for the differential diagnosis between these two forms of autoimmune hypoglycemia is the characterization of the autoantibodies: as a matter of fact, IAA are present in IAS, whereas anti-receptor insulin antibodies are present in type B insulin resistance.[112]

Therapy

The medical treatment of autoimmune hypoglycaemia is problematic for the following reasons: (i) it is not clear whether pharmacologic treatment can be avoided, given the high rates of spontaneous remission; (ii) the whole literature describing the therapeutic approaches consists in scattered case reports or small case series, and no comparison study among the proposed treatment regimens has ever been performed; (iii) predicting factors that allow the identification of patients who benefit most from active treatment have never been searched. The pharmacological options that are currently available include glucocorticoids, somatostatin analogues, diazoxide, azathioprine, rituximab.

However, the indication to a first-line interventional approach for every IAS patient has been questioned, given that the syndrome is mainly a spontaneously-remitting disease.[35] As a matter of fact, approximately 82% of the IAS patients underwent spontaneous remission in a revision of 197 patients diagnosed with IAS from 1970 to 1992:[22] the duration of hypoglycemic episodes was between one and three months in this cohort, without differences according to sex.[22]

Withdrawal of the medication identified as the trigger for the development of IAS seems rational. Nevertheless, the real advantages of the drug discontinuation is unclear provided that no study has ever evaluated the remission rates for patients who withdraw the trigger medication compared to patients who do not.

Besides pharmacological therapies, dietary modifications have been proposed in order to counterbalance the development of hypoglycemic episodes. A rational approach consists in small frequent meals with low carbohydrate content aimed at reducing early postprandial hyperglycaemia and the consequent stimulus to insulin secretion, and at preventing hypoglycemic attacks.[85,91] Treatment with uncooked cornstarch has been successfully applied in the setting of IAS, after originally resulting effective in the setting of glycogen storage diseases.[55] Cornstarch is a glucose polymer slowly absorbed by the gut and able to avoid postprandial glycemic peaks, so the purposes of its administration are somehow overlapped with the suggested dietary regimen consisting in small and frequent meals. Similarly, treatment with alpha-glucosidase inhibitors (acarbose), prevents postprandial hyperglycemia, thus displaying different degrees of benefit in reducing glycemic excursions in IAS.[113,114] In case of severe hypoglycemic episodes, intravenous glucose administration may be necessary, especially in order to prevent nightly glycemic fluctuations.[88]

Among the strategies aimed at reducing insulin release, somatostatin analogues,[40,115] diazoxide[41,115,116] and even pancreatectomy[18,79] have been proposed, with variable results.

Scattered cases have proposed metformin in a combined therapeutic approach to IAS, with the aim to reduce insulin resistance (especially in patients affected by metabolic syndrome) and thus reducing insulin secretion and the consequent formation of insulin-IAA complexes.[36,117] The results of this treatment have not been evaluated systematically.

Given the autoimmune nature of the IAS, this condition has been treated with high-dose corticosteroids, with overall good results.[3,22,34,115] Other immunosuppressive agents, such as azathioprine, have been proposed in case of persistency of the disease despite high-dose systemic corticosteroids.[118] Rituximab is an anti-CD20 monoclonal antibody that has been used for the treatment of severe refractory IAS both alone[119,120] and following immunoadsorption with an adsorber system containing sheep antigens directed against human immunoglobulins.[121] The rational for its use in the setting of IAS comes from the type 1 diabetes immunological intervention trial "TrialNet", which demonstrated that a single course of rituximab produced a complete disappearance of IAA in 40% of patients that were previously IAA-positive, with an effect lasting up to three years.[122]

Plasmapheresis has been used in more severe cases, with the aim to lower IAA titer rapidly, thus preventing hypoglycemia.[113,123,124]

Independently from the kind of therapeutic approach adopted, frequent glucose monitoring during the follow-up seems advisable. Continuous glucose monitoring (CGM) allows glucose measurement in the interstitial fluid with a frequency up to 5 mins, with the possibility of high and low glucose levels alarms and glucose trend information, that has been proven efficacious in diabetic patients in helping reducing HbA1c concentrations.[125] The same tool was successfully applied in IAS,[36,119] given its characteristics that allow a prompter recognition of hypoglycemic episodes and enhance patient's compliance to self-monitoring. However, CGM suffers of a certain delay in

reporting glycemic variations when compared to the direct measurement in the capillary blood through finger-sticks, and this is due to the lag time necessary to equilibrate blood and interstitial glucose concentrations. Flash glucose monitoring (FGM) is another monitoring tool that was applied successfully in the management of IAS.[35] FGM is an intermittently-scanned continuous monitoring system. As a consequence, FGM is a low-cost non-invasive tool, useful for frequent monitoring of glucose concentrations, that enhances the patient self-monitoring by reducing the burden of finger-sticks. Compared to CGM, the pros of the FGM consist in its increased simplicity and lower cost, whereas its cons consist in the absence of an acoustic alarm for hypoglycaemic episodes. On the other hand, the tendency arrows provided by this system may help the patient in preventing downward glycemic fluctuations.[126]

The prognosis of the disease has not been investigated systematically, so no data regarding its survival rate are currently available. The recurrence rate of IAS following its full resolution is low: in the above-mentioned revision of 197 Japanese patients, only nine over 197 patients experienced recurrence of the hypoglycemic episodes, which accounts for a recurrence rate lower than 5%.[22] Recurrence followed re-administration of the triggering drug only in a minority of patients, whereas the majority developed recurrence of the disease without any known triggering factor.[22] Given that recurrence of the disease reappeared even one year following the last hypoglycemic episode, the timing of the correct follow-up is not clear.

Conclusion

Fifty years following its first description, IAS has been extensively reported and many important results have been accomplished in the research regarding this condition. Indeed, nowadays IAS is no longer considered a curious and rare disease mainly originating in Asian patients but has had a worldwide spread and its incidence seems definitely increasing, especially in western countries. This may be due to the wide diffusion of medications and substances that are well-known triggering factors in the pathogenesis of the disease, or to the larger awareness for this condition compared to the past decades. As a consequence, considering IAS in the differential diagnosis of hypoglycemia is nowadays mandatory, even outside the setting of patients of Asian ancestry. The diagnostic approach to IAS is complex, and the gold standard for the differential diagnosis with other forms of hypoglycemia consists in the measurement of insulin autoantibodies. As a consequence, a blood sample for the IAA assay should always be obtained in the suspect of IAS, even before proceeding to potentially useless and costly imaging examinations. If IAA assay is not available, the sample should be preliminarily tested with PEG precipitation, and then eventually sent to a lab that owns the kit for measuring the IAA. Once the diagnosis of IAS has been confirmed, the patients should be evaluated carefully in order to assess the indication to pharmacologic therapy, always taking into account that no study have currently compared different treatment regimens. IAS patients should be monitored thoroughly, both during the active phase of the disease and following its remission. To date, even though the research in this field has accomplished astonishing results, there are still some missing points, especially regarding the pathogenesis of the disease and its management. The need for medical trials that compare different treatment modalities is urgent, even though the recruitment of a sufficient amount of IAS patients is difficult, due to the rarity of the condition.

Disclosure

The authors report no conflicts of interest in this work.

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