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HIRATA SYNDROME- A RARE CASE REPORT

General Medicine

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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 (i.e 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).

KEYWORDS

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 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. 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. The pathogenesis of IAS has been extensively investigated and the mechanisms 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. 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.

Case Report –

A 28 Year Old Male Came To OPD With Chief Complaints Of

- Giddiness since 1 month
- Heaviness of head since 1 month
- Nausea since 1 month

No h/o sleep disturbances.
No h/o constipation .
No h/o Acidity .
No h/o any medication intake.
No h/o DM,HTN,TB, Seizure disorder.
NO h/o any addiction.

Patients father is known case of type 2 DM and on regular medications since 6 years. Apart from this there is no significant family history.

On Further Investigations-

1. Fasting insulin -20.2
2. Post-prandial 1 hour insulin -242.9
3. Post-prandial 2 hour insulin – >300
4. Anti Insulin antibodies – 72
5. Fasting glucose -89
6. Post-prandial 1 hour glucose -177
7. Post-prandial 2 hour glucose – 132
8. Serum Vit B 12- 1547
9. Serum Calcium -9.4
10. Serum Na/K/Cl -142/4.63/101.8
11. Serum Cortisol – 11.7

Based on above investigations patient was diagnosed with HIRATSYNDROME- (INSULIN AUTOIMMUNE SYNDROME) started on Tablet Prednisolone 60mg OD for 10 days and then called for review, On follow up after 10 days he recovered from all symptoms, and we continued omnacortil tapering does for 6-8 weeks.

DISCUSSION –

IAS has been described as a form of type VII hypersensitivity, characterized by the presence of autoantibodies against a circulating antigen. 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; IAA belonging to IgA and IgM are definitely rare, although described. 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. 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. 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. 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.

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.

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. 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, 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.

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.

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