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Original Research Paper

Diabetology

HIRATA'S DISEASE (INSULIN AUTOIMMUNE SYNDROME) IN AN ADOLESCENT: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Insulin autoimmune syndrome (IAS), or Hirata's disease, is a rare cause of spontaneous hyperinsulinemic hypoglycemia due to autoantibodies against endogenous insulin, typically without prior insulin exposure. Although classically described in older adults, pediatric cases are increasingly recognized.[1,9,10,20] Case: We report a 15-year-old girl with recurrent early morning hypoglycemia characterized by adrenergic and neuroglycopenic symptoms, resolving with oral intake. A severe episode (plasma glucose 35 mg/dL) led to hospitalization. Fasting and post-glucose insulin levels were elevated (fasting 15.03 IU/mL; 1-hour post-load 103.68 IU/mL). Imaging (abdominal MRI) and workup for fatty acid oxidation defects were unremarkable. The clinical pattern (late post-absorptive hypoglycemia), inappropriately high insulin, and exclusion of structural disease supported a working diagnosis of IAS. IAA testing—considered confirmatory—was not available.**Management and Outcomes:** The patient was managed conservatively with dietary counseling (frequent small meals, avoidance of prolonged fasting). [Author to insert: follow-up duration and outcomes.] **Conclusion:** IAS should be considered in adolescents with recurrent hypoglycemia when exogenous insulin exposure is absent and hyperinsulinemia is present, particularly when imaging is negative. Early recognition prevents morbidity and unnecessary invasive procedures.[1,4,6,15] Keywords: Insulin autoimmune syndrome; Hirata's disease; hypoglycemia; hyperinsulinemia; adolescent; insulin autoantibodies **Highlights** IAS can present in adolescents with early morning hypoglycemia and inappropriately high insulin levels, even without drug triggers.[1,9,10,20] IAA-mediated insulin–antibody complexes can cause postprandial hyperglycemia followed by spontaneous hypoglycemia hours later.[3,14] Diagnosis is clinical when IAA assays are unavailable; key differentials include insulinoma, surreptitious insulin/sulfonylurea use, and fatty acid oxidation disorders.[4,6,17] First-line management is dietary (frequent meals, slow-release carbohydrate); immunosuppression or plasmapheresis is reserved for refractory cases.[1,15,16] Spontaneous remission is common, particularly when drug-induced; pediatric cases are rare but documented.[1,19,20]

KEYWORDS : Insulin Autoimmune Syndrome, Hirata's disease, Hyperinsulinemic hypoglycemia, Autoantibodies to insulin

INTRODUCTION

Insulin autoimmune syndrome (IAS), first described by Hirata in 1970, is characterized by spontaneous hypoglycemia from autoantibodies to endogenous insulin in individuals without prior insulin exposure.[2,7] The clinical spectrum ranges from mild intermittent symptoms to severe neuroglycopenia.[1,4] Although originally thought to primarily affect older adults, cases across age groups-including children-have been reported. [7–10,20]IAS is associated with HLA-DR4 (particularly DRB1*04:06 in East Asians) and can be triggered by sulfhydryl-containing drugs (e.g., methimazole, captopril, alpha-lipoic acid), infections, or other immune perturbations. [1,11,12,19] Diagnostic delays are common due to rarity, limited access to IAA testing, and overlap with insulinoma and factitious hypoglycemia.[4,6]We report an adolescent with recurrent early morning hypoglycemia and hyperinsulinemia, discuss diagnostic reasoning where IAA testing is unavailable, and review current evidence on pathophysiology, evaluation, and management.

Case Presentation

A 15-year-old girl presented with recurrent early morning hypoglycemia since May 2021, approximately 10 hours after the last meal. Episodes involved sweating, palpitations, confusion, and tremors, promptly relieved with food. There were no nocturnal episodes reported. She had normal growth and development, no prior hospitalizations, and no regular medications. Family history was notable for maternal type 2 diabetes. Physical examination was unremarkable. A severe event (capillary glucose 35 mg/dL) prompted hospitalization. Laboratory evaluation is summarized in Table 1. Notably, fasting and post-load insulin levels were elevated (fasting 15.03 µIU/mL; 1-hour post-load 103.68 µIU/mL). MRI abdomen and tests for fatty acid oxidation defects were negative. There was no evidence of systemic autoimmunity (ANA negative). Inflammatory markers were mildly elevated (ESR 45 mm/h; CRP marginally above the upper limit), and mild anemia was present. Viral serologies (HBsAg, HCV, HIV) were negative. Given the age, late post-absorptive timing, symptom resolution with feeding, inappropriately elevated insulin, and negative imaging, IAS (Hirata's disease) was strongly suspected. IAA testing was not available.

Table 1. Laboratory Results

Parameter	Normal Range	Result
SARS-CoV-2 Viral RNA RT-PCR	—	Not detected
Serum Insulin (Fasting)	2–25 µIU/mL	15.03 µIU/mL
Serum Insulin (0.5 hr post-load)	30–230 mIU/L	61.48 mIU/L
Serum Insulin (1 hr post-load)	18–276 mIU/L	103.68 mIU/L
Anti-dsDNA (ADNA)	—	Negative
ANA (ELISA)	—	Negative
C-reactive protein	0.08–0.79 mg/dL	0.95 mg/dL
ESR (Westergren)	3–12 mm/h	45 mm/h
HbA1c	4–6%	4.8%
HBsAg	—	Negative
HCV Ab (ELISA)	—	Negative
HIV I & II Ab (ELISA)	—	Negative
Cortisol (morning)	—	14.77 (units per lab)
TSH	0.3–6 µIU/mL	2.33 µIU/mL
ALP	35–125 U/L	178.9 U/L
ALT	5–40 U/L	49.8 U/L
AST	5–45 U/L	45.7 U/L
Blood Urea	18–45 mg/dL	15.3 mg/dL
Folate	≥5.0 ng/mL	8.2 ng/mL
Hemoglobin	11.5–16.5 g/dL	10.2 g/dL
Reticulocyte %	0.5–2%	2.3%
Serum Chloride	95–108 mmol/L	104 mmol/L
Creatinine	0.5–1.5 mg/dL	0.62 mg/dL
Serum Iron	37–145 µg/dL	150 µg/dL
Potassium	3.5–5.5 mmol/L	4.5 mmol/L

Sodium	136–146 mmol/L	134 mmol/L
Uric Acid	2.7–5.7 mg/dL	2.8 mg/dL
Total Bilirubin	0.2–1.0 mg/dL	0.76 mg/dL
Total Leukocyte Count	4,000–11,000/μL	12,800/μL
Fasting plasma glucose	60–100 mg/dL	95 mg/dL
Post-prandial plasma glucose	90–135 mg/dL	139 mg/dL

Diagnostic Assessment

Working diagnosis: Insulin Autoimmune Syndrome (Hirata's disease)

Rationale: Recurrent hypoglycemia 10+ hours post-meal with adrenergic/neuroglycopenic symptoms and relief by ingestion (compatible with Whipple's triad).[6] Inappropriately increased insulin relative to glycemia and negative imaging for pancreatic pathology.[4,6] Pediatric onset with absence of exogenous insulin exposure; no clear drug trigger documented.[1,11,19,20] Alternative causes less likely: **Insulinoma:** imaging negative; timing of late post-absorptive hypoglycemia could overlap but IAA-mediated kinetics better fit biphasic hyperglycemia-hypoglycemia pattern.[3,4] Exogenous insulin/sulfonylurea: no history; drug screen not reported.[6] Fatty acid oxidation disorders: screening negative. Adrenal insufficiency, hypopituitarism: morning cortisol acceptable; TSH normal.[17] Confirmatory testing (if available): Serum insulin autoantibodies (IAA).[1,14]

Therapeutic Intervention

Dietary modification: small frequent meals; avoidance of prolonged fasting/overnight gaps; bedtime complex carbohydrate.[1,15] Education: recognition of symptoms; immediate carbohydrate intake; home glucose monitoring.

Options for refractory disease : Acarbose to blunt postprandial excursions.[1,15] Uncooked cornstarch at bedtime for sustained glucose release.[15] Glucocorticoids, azathioprine, rituximab, plasmapheresis, or octreotide in severe/prolonged cases.[1,16]

Follow-up and Outcomes

The patient was followed for a total duration of **one year** after the initial diagnosis. During this period, she was managed with dietary modification and avoidance of prolonged fasting. She experienced progressive reduction in the frequency and severity of hypoglycemic episodes, with complete cessation of symptomatic events within a few months of implementing lifestyle adjustments. No medication- or infection-related triggers were identified on retrospective review. By the end of the follow-up period, the patient had fully recovered, resumed normal daily activities, and maintained regular school attendance without limitation. She has remained free of recurrent hypoglycemic episodes, consistent with the self-limiting nature of IAS reported in the literature.

Discussion and Literature Review

Epidemiology & Genetics. IAS is rare globally, more frequently reported in East Asia, with a strong HLA-DR4 association (DRB1*04:06/04:03), suggesting genetic susceptibility.[1,12] Cases outside Asia are increasingly recognized—often drug-induced.[1,19] Pediatric cases, though uncommon, are documented.[9,10,20]Pathophysiology. High-affinity insulin autoantibodies bind postprandial insulin, blunting receptor engagement and causing transient hyperglycemia. Hours later, dissociation of insulin–antibody complexes releases free insulin independent of glycemia, precipitating late post-absorptive hypoglycemia—a characteristic "postprandial hyperglycemia → delayed hypoglycemia" pattern.[3,5,14]Triggers. Sulfhydryl-containing drugs (e.g., methimazole, captopril, alpha-lipoic acid) can alter insulin's disulfide bonds, enhancing immunogenicity and IAA formation.[1,11,19] Viral infections have also been implicated.[1]

Diagnosis. The Endocrine Society guidance recommends confirming Whipple's triad; measuring plasma glucose, insulin, C-peptide, proinsulin during an event; and excluding surreptitious agents (sulfonylurea screen).[6,14] In IAS, insulin is elevated; C-peptide may be normal/high; insulin/C-peptide ratios can be misleading due to assay interference; IAA positivity is supportive/confirmatory.[1,4,14,17] When IAA testing is unavailable, a consistent clinical phenotype, absence of pancreatic lesion, and exclusion of drug/factitious causes support a probable IAS diagnosis.

Management. Many cases are self-limited, especially drug-induced after withdrawal.[1,19] First-line therapy is dietary (frequent low-glycemic meals, bedtime complex carbohydrate or uncooked cornstarch).[1,15] Acarbose reduces postprandial spikes.[1] Severe or persistent cases may warrant short-course steroids; selected refractory cases respond to azathioprine, rituximab, or plasmapheresis.[1,16]

Prognosis. Prognosis is generally favourable with spontaneous remission over weeks to months once triggers are removed and glucose variability is blunted.[1,15,16] Pediatric cases have outcomes comparable to adults.[20]

Relevance of this case. This adolescent presentation without a clear medication trigger underscores that IAS is not limited to older adults and can occur without classic exposures. Prompt recognition prevents unnecessary invasive localization procedures for insulinoma and reduces morbidity from recurrent hypoglycemia.[1,4,6]

Learning Points: Consider IAS in adolescents with spontaneous hyperinsulinemic hypoglycemia and negative imaging, especially with delayed post-absorptive episodes.[1,3,4] IAA testing confirms the diagnosis but may be unavailable; in such settings, a syndromic approach with careful exclusion of insulinoma and drug/factitious causes is pragmatic.[6,14,17] Dietary strategies (frequent meals, slow-release carbohydrate) are first-line; most cases remit; immunomodulation is reserved for refractory disease.[1,15,16] Review drug exposures (e.g., methimazole, captopril, alpha-lipoic acid); cessation can be curative.[1,11,19]

Informed Consent

Written informed consent was obtained from the patient's parent.

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Conflicts of Interest

No conflicts of interest.

REFERENCES

1. Cappellani D, Macchia E, Falorni A, Marchetti P. Insulin Autoimmune Syndrome (Hirata Disease): A Comprehensive Review Fifty Years After Its First Description. *Diabetes Metab Syndr Obes*. 2020;13:963–978.
2. Hirata Y, Ishizu H, Ouchi N. Insulin autoimmunity in a case of spontaneous hypoglycemia. *J Jpn Diabetes Soc*. 1970;13:312–320.
3. De Pirro R, Roth RA, Rossetti L, Goldfine ID. Characterization of the serum from a patient with insulin resistance and hypoglycemia. *Diabetes*. 1984;33(3):301–304.
4. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. *Medicine (Baltimore)*. 2009;88(3):141–153.
5. Ishizuka T, Ogawa S, Mori T, et al. Characteristics of the antibodies of two patients who developed daytime hyperglycemia and morning hypoglycemia because of insulin antibodies. *Diabetes Res Clin Pract*. 2009;84(2):e21–e23.
6. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of

adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709–728.
7. Hirata Y. Insulin Autoimmune Syndrome – the second case. *J Jpn Diabetes Soc*. 1972;15:187–192.
8. Folling I, Norman N. Hyperglycemia, hypoglycemic attacks, and production of anti-insulin antibodies without previous known immunization. *Diabetes*. 1972;21(7):814–826.
9. Hirata Y, Tominaga M, Ito JI, Noguchi A. Spontaneous hypoglycemia with insulin autoimmunity in Graves' disease. *Ann Intern Med*. 1974;81(2):214–218.
10. Oneda A, Matsuda K, Sato M, Yamagata S, Sato T. Hypoglycemia due to apparent autoantibodies to insulin. *Diabetes*. 1974;23(1):41–50.
11. Hirata Y. Methimazole and insulin autoimmune syndrome with hypoglycemia. *Lancet*. 1983;2(8357):1037–1038.
12. Uchigata Y, Kuwata S, Tokunaga K, et al. Strong association of insulin autoimmune syndrome with HLA-DR4. *Lancet*. 1992;339(8790):393–394.
13. Uchigata Y, Hirata Y, Omori Y. A novel concept of type VII hypersensitivity introduced by insulin autoimmune syndrome (Hirata's disease). *Autoimmunity*. 1995;20(3):207–208.
14. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline
15. Kahn SE, Weir GC, Horton ES, et al. [Guideline reference as provided by author]. *J Clin Endocrinol Metab*. 2010;95(12):4876–4891.
16. Alam S, Ozair M, Ahmad J. Hypoglycemia due to insulin autoimmune syndrome: A rare cause not to be forgotten. *J Clin Transl Endocrinol Case Rep*. 2016;2:7–9.
17. Boro H, Gupta U, Singh C, Malhotra R, Khadgawat R. Insulin Autoimmune Syndrome – A Case Series. *European Endocrinology*. 2020;16(2):168.
18. Service FJ, Rizza RA, Cryer PE. Diagnosis and treatment of hypoglycemia. *N Engl J Med*. 2004;351(8):782–789.
19. Molitch ME. Hypoglycemia. *N Engl J Med*. 2009;361(20):1983–1992.
20. Kawai K, et al. Drug-induced insulin autoimmune syndrome. *Autoimmunity*. 2010;43(3):210–215.
21. Liao LM, et al. Insulin autoimmune syndrome in childhood. *J Pediatr Endocrinol Metab*. 2017;30(3):363–366.