Volume 20 Issue 5
Originally issued as K1

Global Journal of Medical Research: K
Interdisciplinary
Volume 20 Issue 1 Version 1.0 Year 2020
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Insulin Autoimmune Syndrome Treated with Plasmapharesis

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Abstract- A 66-year male with a history of Central Serous Retinopathy presented with recurrent episodes of hypoglycemia. On evaluation, he was found to have insulin-mediated hypoglycemia with serum insulin of 300uIU/ml, C peptide 27.51ng/ml, when the blood glucose was 46mg/dl. High insulin levels above 100uIU/ml, led to suspicion of Autoimmune hypoglycemia and were confirmed by a high anti-insulin antibody titer of 300U/ml. Imaging was negative for Insulinoma. The patient was started on low dose oral prednisolone under ophthalmological monitoring, but as there was no symptomatic improvement, the dose was increased following which there was a flare-up of CSR. The patient was initiated on plasmapheresis following which his hypoglycemia improved with drop in anti-insulin antibody titers to 29U/ml. The patient was maintained on low dose steroids, which were tapered and stopped over the next six months with complete resolution of hypoglycemia and normalization of anti-insulin antibody titers.

Keywords: *hypoglycemia, autoimmune, plasmapheresis, anti-insulin antibody.*

GJMR-K Classification: *NLMC Code: WD 305*



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Insulin Autoimmune Syndrome Treated with Plasmapharesis

Dr. Kavya Jonnalagadda [α] & Dr. Praveen. V. Pavithran [σ]

Abstract- A 66-year male with a history of Central Serous Retinopathy presented with recurrent episodes of hypoglycemia. On evaluation, he was found to have insulin-mediated hypoglycemia with serum insulin of 300uIU/ml, C peptide 27.51ng/ml, when the blood glucose was 46mg/dl. High insulin levels above 100uIU/ml, led to suspicion of Autoimmune hypoglycemia and were confirmed by a high anti-insulin antibody titer of 300U/ml. Imaging was negative for Insulinoma. The patient was started on low dose oral prednisolone under ophthalmological monitoring, but as there was no symptomatic improvement, the dose was increased following which there was a flare-up of CSR. The patient was initiated on plasmapheresis following which his hypoglycemia improved with drop in anti-insulin antibody titers to 29U/ml. The patient was maintained on low dose steroids, which were tapered and stopped over the next six months with complete resolution of hypoglycemia and normalization of anti-insulin antibody titers.

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I. Introduction

Autoimmune hypoglycemia is a rare but key cause of hyperinsulinemic hypoglycemia, which either resolves by itself or will need immunomodulators. This case highlights the usefulness of plasmapheresis when routine treatments like steroids are contraindicated and or ineffective. Lack of awareness of the condition can lead to unnecessary interventions for an insulinoma.

II. Case Presentation

A 66-year male with a history of Central Serous Retinopathy was referred for the evaluation of recurrent episodes of Hypoglycemia occurring in both fasting and postprandial state. Four months before presentation, he had tinnitus for which he had taken alternative medicines and multivitamins following which he experienced recurrent episodes of fatigue, palpitations, sweating, and day time sleep, which went unexplained. Hypoglycemia was diagnosed when he was found unresponsive in the bed early in the morning, which led to emergency room admission and documentation of venous plasma glucose as 38 mg/dl. Physical examination was unrevealing. The patient underwent a supervised fasting test and developed hypoglycemia within four hours of fasting. At this time, venous plasma glucose levels were 46.1 mg/dl, and 32.9 mg/dl, Insulin was 300uIU/ml, C-peptide was 27.51ng/ml. High insulin levels more than 100uIU/ml led to suspicion of autoimmune hypoglycemia and confirmed with high levels of anti-insulin antibody titers >300U/ml. The imaging of the pancreas was normal. HLA typing was not done. The patient was started on a low dose of oral prednisolone 20 mg OD, but as the patient continued to have episodes of hypoglycemias the strength of steroids has been increased to 40 mg/day with which the hypoglycemic symptoms improved, but the patient had flare-up of Central Serous Retinopathy, and the ophthalmologist advised to decrease the dosage of steroids. In view of this, a trial of plasmapheresis was initiated, and he underwent six sessions on alternate days following which anti-insulin antibody titers have dropped to 29U/ml, and the frequency of hypoglycemic episodes still reduced. The patient was maintained on low dose steroids, which were tapered and stopped over the next six months. Presently the antibody titer has dropped to 1.3U/ml. Currently, he is free of hypoglycemic symptoms.

III. Discussion

Hirata disease or Insulin autoimmune syndrome (IAS), is a rare cause of hyperinsulinemic hypoglycemia with autoantibodies to native insulin in individuals without prior exposure to exogenous insulin.[1] More than 300 cases of Insulin autoimmune syndrome were published.[2]Highest number was recorded in Japan, followed by Europe and the US.[3] In these patients, the cause of hypoglycemia was due to the binding of the antibodies to the endogenous insulin, which leads to increased levels of bioavailable insulin, which were physiologically inappropriate, causing either hyper or hypoglycemia. [4] More than half of IAS patients had recent exposure to drugs containing a sulfhydryl group. [5]Methimazole, is the most common trigger for IAS. Other drugs that can cause IAS include imipenem, penicillins, isoniazid, glutathione, carbimazole, tolbutamide, D penicillamine, Interferon-alpha, procaine-mide. There are many other drugs that can cause IAS, but the above-mentioned drugs are common drugs that can provoke IAS.[6] Alpha-lipoic acid, a health supplement with antioxidant and anti aging properties used in the treatment of neurological symptoms of diabetes, was associated with IAS in recent years.[7]

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IAS is a transient condition with spontaneous resolution within 3–6 months of diagnosis in the majority of the patients.[8]Small frequent meals low in carbohydrates remain the first line of treatment in those with intractable hypoglycemia. Drugs responsible for hypoglycemia, if present, should be stopped. Glucocorticoids are the mainstay of treatment. Other therapeutic options include acarbose, which delays carbohydrate digestion and absorption, plasmapheresis to reduce insulin autoantibody titers. All these therapeutic options have demonstrated varying success in the management of IAS.[4][9] If hypoglycemia persists, combination therapy with Glucocorticoids and immunosuppressants like azathioprine or 6-mercaptopurine along with plasmapheresis should be considered.[9]In our patient as there is a flare in the CSR steroids could not be continued at a higher dose and we opted to go ahead with a combination of steroids and plasmapheresis with which we were able to come down on the dose of steroids following which his ocular symptoms and hypoglycemic symptoms have improved. An anti-CD20 monoclonal antibody Rituximab, which acts by blocking antibody responses and suppress insulin autoantibodies, is the last hope for those with refractory hypoglycemia.[10]

IV. Conclusion

1. Autoimmune hypoglycemia is one of the usual causes of hyperinsulinemic hypoglycemia if drug-induced etiology could be ruled out
2. High insulin levels >100uIU/ml during documented hypoglycaemic episodes should initiate workup for autoimmune etiology as insulin is rarely above 100uIU/ml in insulinomas.
3. Spontaneous remission is seen in up to 80% of patients.
4. Most patients respond to steroids.
5. Plasmapheresis is a second line therapy which is beneficial in many patients, although the effect may be delayed.

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