Original Article

Insulin Autoantibody Syndrome: Varying Clinical Presentations and Response Patterns of an Underrecognized Entity

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Abstract

Context: Insulin autoantibody syndrome (IAAS) is considered to be a rare cause of hyperinsulinaemic hypoglycaemia. Lack of familiarity with the varied clinical manifestations leads to underdiagnosis. Localization techniques aimed at insulin-secreting neoplasms and nesidioblastosis, which are expensive often are ordered when the correct diagnosis is not made. **Aims:** We describe the myriad of clinical manifestations associated with IAAS based on single centre experience. **Settings and Design:** Retrospective analysis of patients who got admitted with symptoms suggestive of hypoglycaemia and underwent mixed meal test and prolonged hypoglycaemic test from 2016 to 2019. **Subjects and Methods:** Retrospective data of 12 patients with IAAS who were diagnosed in the threeyear time period between 2016 and 2019 are included in this analysis. Clinical details, biochemical parameters and imaging modalities were analysed. **Statistical Analysis:** All analyses were performed with SPSS software (version 17). **Results:** Total of twelve patients 12 (5 male and 7 females) were identified as IAAS. Median age of presentation was 57 years. Median insulin levels and median C-peptide levels were 300 miu/ml and 18.5 ng/ml respectively. Only 3 (25%) patients had spontaneous resolution. Steroid induced remission occurred by 3 months in the remaining patients. Intermittent hyperglycaemia was seen in 9 (75%) patients. Implicatable drug use preceding the occurrence of the clinical symptoms was observed in five patients. **Conclusion:** IAAS is not uncommon in India. The diagnosis should be pursued in patients with hyperinsulinaemic hypoglycaemia especially when insulin levels are very high or when there is intermittent hyperglycaemia.

Keywords: C-peptide levels, insulin, Insulin autoantibody syndrome

Introduction

Insulin autoantibody (IAA) syndrome is a rare autoimmune disorder first described by Hirata *et al*. in 1970 in Japanese population.[1] Case reports from other parts of the world including India seems to suggest an increasing awareness of the disease entity.[2] Classically it is described as a disorder manifesting with recurrent episodes of hyperinsulinaemic hypoglycaemia with unsuppressed c-peptide values and high titres of IAAs.[3] Literature is replete with case reports suggesting severity varying from mild to potentially life-threatening symptoms. Spontaneous remission is described in approximately 80% of patients.[3] Rest of the patients were found to respond to pharmacological agents commonly steroids and rarely other immunosuppressive or immunomodulatory agents like azathioprine or rituximab. Plasmapheresis has also been tried in few cases with reported benefit.[3,4] We had previously published our case series of eight patients with IAA syndrome.[5] The number of patients has since grown and this article attempts to put forth our experiences and new insights in the last 3 years since the publication of the original case series. Awareness of myriad of presentations of this disorder can potentially avoid costly localization techniques currently employed as part of evaluation of hyperinsulinaemic hypoglycaemia.

Subjects and Methods

Patients diagnosed as definite IAAS between 2016 and 2019 were included in this study. Diagnosis of definite IAAS was made if they met the following criteria.

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1. Recurrent episodes of symptomatic hyperinsulinaemic hypoglycaemia with nonsuppressed c-peptide with venous plasma glucose less than 55 mg/dl as per standard definitions
2. High titres of insulin autoantibody above the normal upper limit cut off for the assay.
3. Nondiabetic without prior exposure to insulin or oral hypoglycaemic agents
4. No history of bariatric surgery.

Severity of presentation was graded based on frequency of hypoglycaemic symptoms and whether it was severe enough to cause alteration of sensorium. Presentation was categorized as mild when hypoglycaemic episodes as evidenced by hyperadrenergic symptoms were present at a frequency of less than one per day. At least daily symptoms were categorized as moderate. Any hypoglycaemic episode causing obtundation of sensorium was graded as severe.

Details of evaluation

Patients without diabetes presenting with symptoms and biochemistry suggesting hypoglycaemia underwent mixed meal testing following by prolonged fasting as per standard protocol.[6] Insulin and c-peptide levels were sent at the time of hypoglycaemia (RBS <55 mg/dl). Insulin antibody measurement was also done. MDCT abdomen with pancreatic protocol was done in 10 patients with unsuppressed insulin and C-peptide. Serum protein electrophoresis was done in elderly patients to rule out myeloma. Antinuclear antibody testing (ANA: Immunofluorescence) was ordered in patients who complained of musculoskeletal/joint symptoms.

Biochemical investigations

Insulin was estimated by chemiluminescent microparticle immunoassay with an analytic sensitivity of <1 μIU/mL. C-peptide was estimated by electrochemiluminescence immunoassay on the Elecsys system (Roche Diagnostics, Mannheim, Germany) with an analytical sensitivity of 0.01 ng/mL. IAAs were estimated by radiobinding assay (RBA; positive >0.4 U/ml) in Quest Diagnostics (Nichols Institute, San Juan Capistrano, CA) or in DDRC labs by enzyme-linked immunosorbent assay (ELISA; positive: >15 U/mL).

Results

Twelve (five male and seven females) patients were identified who were classifiable as definite IAAS. Median age at presentation was 57 years.

Patients presented with either isolated post prandial hypoglycaemia or a combination of postprandial and fasting hypoglycaemia [Table 1]. Median duration of symptoms at presentation was 1 month.

Nine (75%) patients had intermittent hyperglycaemia, which was apparent during glucometer-based monitoring or was demonstrable in the mixed meal testing as postprandial, glucose values above 140 mg%. Insulin and C-peptide levels at the time of hypoglycaemia level varied from 14 to 18200 miu/ml (Median 300) and 7 to 40 ng/ml (Median 18.5) respectively. Except four patients all patients had IAA levels higher than the upper measurable limit of the assay. Ten patients underwent MDCT pancreas which did not reveal any significant abnormality. Three (25%) patients underwent spontaneous remission, whereas the rest received treatment with prednisolone at doses varying from 30 to 60 mg (0.5 to 1 mg/kg/day). Remission occurred within 3 months in patients who were treated with steroids. Patient no 4 developed central serous retinopathy while on steroids necessitating cessation of steroids. He underwent 6 sessions of plasmapheresis, which induced clinical remission and decrease in antibody titres from 300 at diagnosis to 1.3 U/ml.

7/12 (58.3%) required treatment with dextrose infusion to prevent recurrent hypoglycaemia attacks. Some of the atypical presentations other than just hypoglycaemic episodes are detailed below.

Patient 1 was referred to us with first time detected insulin refractory hyperglycaemia with blood glucose values of above 500 mg%. Ketones were negative, but poor

Table 1: Clinical details

Age	Severity	Duration (months)	Fasting hypo	Post hypo	Int hyper	drug	MDCT	0 h	1 h	2 h	3 h	4 h	5 h
49/F	Moderate	0.25	No	Yes	Yes	No	NA	ND	ND	ND	ND	ND	ND
68/F	severe	1.00	No	Yes	No	No	Normal	ND	ND	ND	ND	ND	ND
63/M	Mild	1.00	No	Yes	Yes	No	atrophic pancreas	101	176	207	196	51	50
70/M	severe	1.00	Yes	NA	Yes	yes (A)	Normal	160	185	146	46	32	ND
46/M	Mild	1.00	Yes	No	Yes	No	NA	ND	ND	ND	ND	ND	ND
44/F	Moderate	1.00	Yes	Yes	Yes	Yes (A)	Normal	65.5	271	201	106	53	271
73/F	severe	1.60	Yes	No	Yes	yes (A)	Normal	59.3	209	177	97	59	33
67/F	Mild	0.50	Yes	No	Yes	No	Normal	50	177	171	92	67	34
58/F	severe	1.00	yes	No	Yes	No	Normal	30	258	212	141	68	30
76/M	Moderate	0.50	Yes	Yes	Yes	yes (A)	Normal	60.8	209	256	230	155	76
49/M	Mild	3.00	Yes	Yes	No	Yes (C)	Normal	ND	ND	ND	ND	ND	ND
26/F	severe	1.00	NA	Yes	No	No	Normal	NA	128	128	72	62	75

NA: Not available, ND: Not done

response to subcutaneous boluses leads to initiation of insulin infusion and search for causes of insulin resistance including infection, all of which were noncontributory. She required intravenous insulin infusion initially at a dose of more than 100 units/hour for achieving glycaemic control. After the initial response patient started having persisting hypoglycaemia in both fasting and postprandial on minimal doses of subcutaneous insulin, which was eventually stopped. Serum insulin and c-peptide given at the time of documented hypoglycaemia (venous plasma glucose <55 mg%) was suggestive of endogenous hyperinsulinaemia [Table 2] and insulin antibodies administered were elevated, she responded very well to oral steroids which could be tapered and stopped over a periods of 3 months. She had paraesthesias at the time of discharge which was attributed to hyperglycaemia. Within a short span of 3 months she developed quadriparesis which was diagnosed as Guillain–Barre syndrome based on clinical findings and nerve conduction study suggestive of sensoriaxonal type of motor neuropathy. She responded after 6 sessions of plasmapheresis and is currently fully recovered and off all medications.

Patient 11

A 47-year old male was on irregular antithyroid medications (Carbimazole and propranolol) for Graves' disease (July 2015) for 2 years. He developed loss of consciousness with tonic posturing (June 2017) for which he was hospitalised and found to have hypoglycaemia (blood glucose 35 mg%). On evaluation found to have elevated c-peptide levels [Table 2] at the time of hypoglycaemia. Insulin levels done outside were not available.

Consideration of insulinoma elsewhere led to further investigations including contras-tenhanced CT scan of abdomen and endoscopic ultrasound both of which were inconclusive. IAAS induced by antithyroid drug was considered when the patient was first seen on an OPD basis, IAA was ordered and antithyroid drug was stopped. Since positive result with convincingly high titre was available at the time of admission further supervised fasting was not pursued and further episodes of hypoglycaemia did not recur during his inpatient stay in hospital. He underwent total thyroidectomy for Graves' disease and has remained symptom-free ever since.

Discussion

IAAS is thought to be a rare cause of hyperinsulinaemic hypoglycaemia mostly seen in patients of South East Asian[7] origin. Description of the entity from rest of the world is mostly limited to isolated case reports and small case series.[8,9] During the 3-year period detailed in the methods, we came across 12 patients of IAA syndrome, whereas only 10 patients with confirmed insulinoma were encountered. Our experience seems to suggest that IAA syndrome is a common cause of hyperinsulinaemic hypoglycaemia. In its mildest form IAA syndrome presents as isolated postprandial symptoms (as in patient number 12) characterised by diaphoresis, jitteriness and presyncope which gets relieved with carbohydrate intake. We wonder whether many of the patients with similar presentation were labelled as reactive hypoglycaemia in the past. As spontaneous remission occurs in significant number of patients, the diagnosis might have been overlooked.

Urine Sulfonylurea estimation was not performed in urine samples for any patient as we considered it unnecessary in the light of insulin antibody titres being very high and several patients demonstrating postprandial glucose values in the prediabetic/diabetic ranges on mixed meal testing which would be highly unusual with oral hypoglycaemic agent induced factitious hypoglycaemia. However we agree that in settings where there are no resource limitations estimation of sulfonylurea/oral hypoglycaemia agents in urine is sound practice. Our data seem to suggest that 9 (75%) have biochemically proven intermittent hyperglycaemia (random glucose values more than 140 mg%) which was apparent at the time of presentation or was demonstrable

Table 2: Laboratory parameters and response patterns

Insulin (uIU/ml)	C-peptide (ng/ml)	Insulin antibody U/mL	Remission	Steroid dose	Steroid duration (weeks)	Time to resolution (weeks)
1000.00	26.70	>50	Steroid use	60.00	12	12
1000.00	7.20	>50	Steroid use	40.00	52	52
1000.00	11.50	>50	Spontaneous	0	0	4
300.00	24.39	>300	Steroid use	20.00	20	20
300.00	40.00	>300	Steroid use	30.00	4	24
1000.00	10.39	92.00	Steroid use	30.00	fu	fu
18200.00	32.20	>50	Steroid use	48.00	8	8
300.00	12.90	>50	Steroid use	30.00	15	15
300.00	10.91	228.20	Steroid use	30.00	8	8
300.00	24.12	>300	Steroid use	40.00	4	4
NA*	12.40	219.50	Spontaneous	0	4	8
13.60	26.70	18.00	Spontaneous	0	0	3

*eventhough serun insulin levels are not available patient was included as it is a very good learning example.
Insulin and c-peptide done at RBS<55 mg/dl. Serum electrophoresis was done and found to be normal in patient number 2, 4, 9. Antinuclear antibodies were done and were found to be positive in patient number 1, 4, 12. FU-On follow-up

during mixed meal testing. This is a glycaemic pattern which is not observed with most other hypoglycaemia-related entities except glycogen storage disorders. In resource limited setting this intermittent hyperglycaemic response, in a nondiabetic patient though subtle may obviate the need for sulfonylurea estimation which is advocated by endocrine society.[6] Hyperglycemia as the chief presenting feature is classically part of type B insulin resistance syndrome, which is ascribed to insulin receptor antibodies. It has also been described to occur in insulin-treated patients with extremely high and low glucose values.[9] We have been able to demonstrate extreme insulin resistance and hyperinsulinaemic hypoglycaemia with elevated C-peptide in patient 1. Although we did not estimate insulin receptor antibodies subsequent resolution of glycaemic fluctuations after a course of steroids seems to suggest a role for the antibodies in the fluctuations.

Insulin levels at the time of hypoglycaemia are classically noted to be very high in IAA syndrome usually more than 100 μIU/mL.[3] While in the current series most patients had insulin levels consistent with the previous statement except patient no 12 had a level of 13 μIU/mL. This patient had isolated postprandial symptoms with demonstrable hypoglycaemia which resolved over the course of 2 months. She was advised frequent low-glycaemic index feeds. All patients with frequent symptoms were prescribed steroid with at least partial response with a significant reduction in the frequency of hypoglycaemic attacks within a week.

Dietary manipulation in the form of limited simple carbohydrate intake and frequent intake of complex carbohydrate was instituted in all patients. Uncooked corn starch was used at night at a dose of 1.5 g/kg dissolved in milk or water in few patients. In our experience this measure was not very effective. Modified corn starch has reported as being effective in some reports.[10] Only 25% (3/12) of patients showed spontaneous resolution. This is less than what is reported in world literature.[11]

Patients with moderate-to-severe symptoms responded to dose of steroids varying from 0.5 to 1 mg/kg per day which was tapered and stopped over 2 to 3 months. Most patients responded within a week with significant decrease in frequency and/or severity of hypoglycaemic episodes. Plasmapheresis is described in literature as an effective treatment modality. We used it in patient no 4 as he developed unacceptable side effects to steroids.

Five patients had history of consumption of drugs known to be implicated in IAAS (patient no 4, 6, 7, 10, lipoic acid, patient no 11 carbimazole). Role of antithyroid drugs and lipoid acid in inducing IAAS is well reported in literature.[12,13] Sulfhydryl group seems to be the responsible chemical moiety.

Literature is replete with association of IAAS with autoimmune disease[4,14] and haematological malignancies. ANA screening done in joint-related symptoms was positive for two patients. However none of them had a clearly classifiable rheumatological syndrome. Patient number 1 had an unusual presentation which is consistent with what has been listed as autoimmune overlap in western literature.[15] While steroids caused remission of the IAAS she went on to develop another autoimmune condition which required use of plasmapheresis.

Except in patient 1 follow-up insulin antibody titre estimation (showing decrease in titres) was not performed. This is a draw back of the current series. However very high titres of the antibodies and response to steroids seem to strongly suggest a causative role for these antibodies in the clinical presentation of the patients described.

Conclusion

IAA is probably the most common cause of hyperinsulinaemic hypoglycaemia in nondiabetic individuals. Intermittent hyperglycemia is a hall mark of this disorder and is a valuable clue pointing towards diagnosis. Insulin levels are not always very high as classically described in western and Japanese literature. Most patients without spontaneous resolution respond to steroids.

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Conflicts of interest

There are no conflicts of interest.

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