Original Article

Spontaneous Hypoglycaemia due to Insulin Autoimmune Syndrome in Six Cases, Response to Steroid Therapy and Rituximab

Chandar M. Batra, Savita Jain[1], Kiran P. Kumar[2], Monika Goyal[3], Varsha Kachroo, Simran Takkar, Rini Yadav

Department of Endocrinology, Indraprastha Apollo Hospital, New Delhi, [1]Endocrinology Deep Hospital, Ludhiana, Punjab, [2]Department of Endocrinology, All India Institute of Medical Sciences, New Delhi, [3]Department of Endocrinology, Batra Hospital and Medical Research Centre, New Delhi, India

Abstract

Introduction: Dr. Hirata of Japan first described insulin autoimmune syndrome (IAS) in 1970. Seven hundred ninety-five cases of this rare syndrome have been reported from Japan and China and 29 from India. IAS has the following characteristic features 1) severe spontaneous attacks of hyperinsulinemic hypoglycaemia, 2) high total immunoreactive insulin levels, 3) elevated insulin autoantibody (IAA) titres, 4) no prior exposure to exogenous insulin, and 5) no pathological abnormalities of the pancreatic islet cells. **Methods:** We treated six cases of IAS with high doses of prednisolone for 4-6 weeks and then gradually reduced the doses. Diagnosis of IAS was established by documenting Whipple's triad of symptoms and signs of hypoglycaemia, blood sugar <55 mg/dl, improvement of symptoms with dextrose infusion, inappropriately increased insulin levels >3 uU/ml, C-peptide levels >0.6 ng/ml, and increased titres of anti-insulin autoantibodies. Insulinoma and non-pancreatic tumours were ruled out by CECT (contrast-enhanced computerised tomography) or MRI (magnetic resonance imaging) of the abdomen and if necessary endoscopic ultrasonography and gallium 68 Dotanoc PET (positron enhanced tomography). Autoimmune screening and serum electrophoresis were done to rule out multiple myeloma. Monitoring of the patient's blood sugars was done by the laboratory, glucometer readings, and a freestyle libre glucose monitoring system. **Results:** Remission of hypoglycaemic episodes, hyperglycaemic episodes, and marked reduction of serum insulin and insulin autoantibodies in four out of six patients with diet therapy and steroids. Two patients resistant to steroids were treated with rituximab successfully. Patient 6 developed serious complications of cytomegalovirus and *Pneumocystis carnii* after rituximab, which were treated successfully. **Conclusion:** A careful history including recent infections, medications, and vaccinations provides vital clues in the evaluation. An increased awareness of IAS will prevent unnecessary and costly investigations and surgery. Although it is often self-remitting, steroids are contributory in severe cases. Immunosuppressives are used successfully in cases refractory to steroids. Continuous glucose monitoring system (CGMS), by freestyle libre glucose monitoring system, provided real-time blood sugar values, total time in hypoglycaemia, and total time in the range (TIR), which proved very valuable in managing IAS patients. Low CGMS values should be corroborated clinically and with laboratory or glucometer values.

Keywords: Autoimmune hyperinsulinism, glucocorticoids, hirata disease, insulin autoantibodies, rituximab, spontaneous hypoglycaemia

Introduction

Dr. Hirata of Japan first described insulin autoimmune syndrome (IAS) in 1970.[1] Seven hundred ninety-five cases of this rare syndrome have been reported from Japan and China and 29 from India.[2-5] IAS has the following characteristic features: 1) severe spontaneous attacks of hyperinsulinemic hypoglycaemia 2) high total immunoreactive insulin levels, 3) elevated insulin autoantibody (IAA) titres, 4) no prior exposure to exogenous insulin, and 5) no pathological abnormalities of the pancreatic islet cells.[3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_378_23

Insulin autoantibodies are polyclonal immunoglobulin G-type antibodies. Insulin-insulin antibody complexes are

Address for correspondence: Dr. Chandar M. Batra, Department of Endocrinology, Indraprastha Apollo Hospitals, New Delhi, India.
E-mail: chandarmohanbatra@gmail.com; chandarbatra@yahoo.com

Submitted: 26-Sep-2023 **Revised:** 10-Feb-2024
Accepted: 15-Feb-2024 **Published:** 26-Jun-2024

How to cite this article: Batra CM, Jain S, Kumar KP, Goyal M, Kachroo V, Takkar S, *et al*. Spontaneous hypoglycaemia due to insulin autoimmune syndrome in six cases, response to steroid therapy and rituximab. Indian J Endocr Metab 2024;28:295-301.

created when they bind insulin. As a result, there is less free insulin available, which raises blood sugar levels and prompts beta cells to produce more insulin. Hyperinsulinemic hypoglycaemia results from the antibodies' abrupt insulin release once they have reached the limit of their binding capacity. This insulin release can happen throughout the day and is unrelated to meals. It results in hypoglycaemia at any time of the day. The liver's ability to produce ketones, gluconeogenesis, and glycogenolysis is inhibited by hyperinsulinemia, which makes hypoglycaemia more severe. Recurrent hypoglycaemic episodes impair the counter-regulatory response to hypoglycaemia, leading to hypoglycaemia unawareness.[2-5]

Drugs and viral infections are among the environmental variables that might trigger the condition, although it has a genetic propensity.[2,3] The sulphydryl (SH) group is present in the drugs or their metabolites [Table 1]. The insulin molecule's disulphide bond is broken by the SH group, rendering it antigenic. This triggers the production of insulin autoantibodies by B lymphocytes.[2] We describe the clinical presentations, diagnosis, and management of six cases of IAS.

Table 1: Factors triggering autoimmune insulin autoantibodies in IAS

Drugs	Drugs	Viruses
Methimazole, propyl uracil	D penicillamine	Chickenpox
Alpha lipoic acid	Hydralazine	Mumps
Gliclazide	Clopidogrel	Rubella
Captopril	Pantoprazole	Hepatitis C
Penicillin G	Methionine	Measles
D penicillamine	Glutathione	
Imipenem	Mercaptans	
Isoniazid		

Table 2: Symptoms of hypoglycaemia in six cases of IAS

Symptom	Patient number	Symptom	Patient number
Blurring of vision	1	Palpitation	3,4,6
Loss of consciousness	1,2	Transient loss of power in right hand twice	5
Convulsions	1	Shortness of breath	4
Sweating	1,2,3,4,6	Generalized weakness	3,4
Feeling cold and clammy	1	Anxiety	4
Tremors	6	Dry mouth	4
Dizziness	2,6		

Materials and Methods

We are describing six cases who presented with recurrent attacks of severe hypoglycaemia [Tables 2, 3A, 3B]. They were nondiabetic and had no access to oral hypoglycaemic agents. Their haemoglobin, total and differential counts, renal, and liver functions, and cortisol were normal. Diagnosis of IAS was established by documenting Whipple's triad of symptoms and signs of hypoglycaemia, blood sugar <55 mg/dl, improvement of symptoms with dextrose infusion, and inappropriately increased levels of insulin >3 uU/ml, and C-peptide levels >0.6 ng/ml according to the blood glucose levels and increased titres of insulin autoantibodies.[6] This is necessary to prove hyperinsulinemic hypoglycaemia. Insulinoma and non-pancreatic tumours were ruled out by CECT (contrast-enhanced computerised tomography) or MRI (magnetic resonance imaging) of the abdomen and if necessary endoscopic ultrasonography and gallium 68 Dotanoc PET (positron enhanced tomography). Autoimmune screening and serum electrophoresis were done to rule out multiple myeloma [Tables 3A and 3B]. Monitoring of the patient's blood sugars was done by 2 hourly glucometer readings and a freestyle libre glucose monitoring system.

Case 1

A 79-year-old woman presented to another tertiary care hospital with the blurring of vision, unconsciousness, and convulsions, where she was treated with dextrose infusion for severe hypoglycaemia. She had been taking atenolol and aspirin for hypertension and coronary artery diseases. She had experienced similar episodes in the past month, which were relieved with 25% dextrose. Serum insulin level at 44 mg/dl blood sugar was 9470 uU/ml (*n* = <3 uU/ml) and insulin antibodies were 1070 U/l (*n* = <7). Endoscopic ultrasound in the distal pancreas showed a 4 mm hypoechoic area. The patient underwent a distal pancreatectomy for insulinoma. Hypoglycaemic episodes subsided. No tumour was found on histopathology of the pancreas, and serum insulin levels after pancreatectomy were still 870 uU/ml. She was symptom-free and euglycaemic for three years. She developed an upper respiratory tract infection, which was treated with tablet amoxicillin-clavulanic acid for 10 days.

One month later, she started having episodes of sweating and feeling cold and clammy. Her blood sugar fluctuated between 400 and 34 mg/dl, with severe hyperglycaemia in the evening and hypoglycaemia in the morning. She was admitted at 7 am with cold, clammy skin, sweating, numbness, and tingling all over the body. There were no tremors. Her pulse rate was 90/min, and her BP was 130/80 mm. She was conscious but disoriented to time, place, and person with no focal neurological deficit. Her blood sugar was 34 mg/dl, serum insulin was 39440 uU/ml (n = 3 uU/ml), and C-peptide levels were 87.5 ng/ml (n = 0.6), HbA1c-7%. MRI sella was normal. Insulin autoantibodies were positive >100 u/ml (ref range <1), free insulin <2.5 uu/ml (ref. range 4.0-20.0). The autoimmune screening was negative, and serum electrophoresis and bone marrow biopsy were negative for multiple myeloma and polyclonal gammopathy [Tables 2, 3A, 3B].

Table 3A: Six cases of IAS, clinical picture, and investigations

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/sex	79/F	61/F	41/F	67/F	73/M	60/M
Blood sugar (mg/dl)	34	52	50	23	24	40
Insulin levels (*n* <3 uU/ml)	39440	3000	2489	24000	7512	17925
C-peptide levels (*n* <0.6 ng/ml)	87.5	4.35	19.19	16.2	18	23.87
Insulin antibodies (*n* <12 units/ml)	1070	360	>300	87.2	140.1	300
Treatment received	Diet, Steroid, Acarbose	Diet, Steroid, Diazoxide	Diet, Steroid	Diet, Steroid, Rituximab	Diet, Steroid	Diet, Steroid, Rituximab
Drug history	Amoxicillin-clavulanic acid	Aceclofenac	None	None	Clopidogrel	Covid Vaccine
After remission insulin levels (*n* ≤3 Uu/ml)	2000	45	200		600	
After remission antibody levels (*n* ≤12 Units/ml)		<12	20	1.53		

Table 3B: Six cases of IAS, clinical picture and investigations

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Imaging	CECT abdomen, Endoscopic Ultrasound	CECT abdomen, Endoscopic Ultrasound	CECT abdomen, Gallium 68 Dotanoc PET scan	CECT abdomen, Gallium 68 Dotanoc PET scan		
Se protein electrophoresis	Negative	Polyclonal gammopathy	Negative	Negative	Negative	
ANA	-	-	-	-	-	+
Anti-DsDNA	-	-	-	-	-	-
RA factor	-	-	-	-	-	-
Cortisol	N	N	N	N	N	N
Thyroid function tests	N	N	N	N	N	N
Renal/liver function tests	N	N	N	N	N	N

Diagnosis

IAS due to insulin autoantibodies.

Treatment

We prescribed a 1600 kilocalories low carbohydrate, high protein, high-fat diet, and 100 mg hydrocortisone eight hourly for a day, followed by 40 mg of prednisolone daily and 100 mg of acarbose thrice daily. Hypoglycaemic episodes decreased within three days, but she developed severe hyperglycaemia, with sugars going up to 500 mg/dl, treated with metformin sustained release 1 g twice daily and insulin infusion for one day. Blood sugar levels stabilized after 5 days to 90-96 mg/dl at 8 am, 100-150 mg/dl at 1 pm, and 200-387 mg/dl at 9 pm. Serum insulin reduced from 13470 uU/ml to 2000 uU/ml in 8 days. Prednisolone was given in a dose of 40 mg for 1 month tapered off in 6 weeks. On follow-up for 8 years, she remained euglycaemic.

Case 2

A 61-year-old woman presented with profuse sweating and unconsciousness. She was hypoglycaemic (blood sugar 30 mg/dl) and recovered after intravenous dextrose. Subsequent blood sugar monitoring showed recurrent hypoglycaemia with profuse sweating and dizziness, both fasting and postprandially, relieved with oral glucose. She was on atenolol 25 mg for 10 years for hypertension. Fifteen days before the onset of these symptoms, she was given aceclofenac and paracetamol for pain in both feet. Her BMI was 27.76 kg/m^2, and her blood pressure was 140/90 mm hg. Her systemic examination was normal. We found elevated serum insulin >3000 µU/ml (normal <3 µU/ml) with a fasting blood glucose of 54 mg/dl. Highly sensitive insulin antibodies were positive 36 nmol/L (normal, 0-0.02 nmol/L). While undergoing a 72-hour fast, she developed symptomatic hypoglycaemia with vertigo and generalized weakness after 60 hours (RBS = 50 mg/dl). The corresponding insulin levels of 700 µU/ml and C-peptide of 4.35 ng/ml established endogenous hyperinsulinism.

The autoimmune screen was negative. Serum protein electrophoresis revealed a polyclonal gammopathy [Tables 2, 3A, 3B].

She was discharged on a tablet of diazoxide 100 mg twice daily and prednisolone 60 mg/day for a month and was advised to regular blood sugar monitoring. She responded with a significant reduction in hypoglycaemic events, but postprandial blood sugar increased. So, she was prescribed a low-carbohydrate diet. On follow-up, there were no further hypoglycaemic episodes. Prednisolone tapered off slowly in 4 weeks. On follow-up for 3 years, she is euglycaemic.

Case 3

A 41-year-old woman presented with palpitations, sweating, and generalised weakness. She had similar complaints in the past 3 days, which subsided after taking sugar. Her random blood sugar was 49 mg/dl, and a 25% dextrose

infusion led to an improvement in symptoms. Her physical examination was unremarkable. Her fasting serum insulin was 2489 uU/ml (n < 3), and C-peptide levels were 19.19 ng/ml (n <0.6) at a blood sugar value of 50 mg/dl. Insulin antibody levels were high >300 U/ml (N <12) [Tables 2, 3A, 3B]. Our diagnosis was IAS. She was prescribed a complex carbohydrate diet and prednisolone 60 mg per day. Glucose monitoring with a glucometer was done 6 times daily. Steroids were tapered over three months. No relapse of hypoglycaemic episodes occurred in three months. At the end of the treatment, serum fasting insulin levels decreased to 45 uU/ml and anti-insulin antibody titres to 20 U/ml. The patient is under regular follow-up and has been in remission for three years.

Case 4

A 60-year-old woman was admitted to a local hospital with complaints of difficulty in breathing, anxiety, palpitation, dry mouth, and sweating [Table 2]. She had a known case of primary hypothyroidism on 75 µg thyroxine and hypertension on amlodipine 5 mg daily. Her pulse rate was 90/min, and her BP was 170/100 mm/hg. The systemic exam was within normal limits. There was no neurological deficit. Her blood sugar was 34 mg/dl, and her symptoms were immediately relieved with 100 cc of 10% dextrose. She had 2-5 attacks of severe hypoglycaemia with blood sugars between 30 and 40 mg/dl for the next 30 days. She was admitted under our care at this stage.

We proved hyperinsulinemic hypoglycaemia. At a blood sugar of 23 mg/dl, her serum insulin was 24000 uU/ml (normal <3) [Tables 3A, 3B]. Insulinoma was ruled out by a negative CECT abdomen and a 98 gallium dotanoc PET scan. We made a diagnosis of IAS.

She was treated with a low carbohydrate diet divided into six meals per day, prednisolone 60 mg once a day, octreotide 50 mcg, diazoxide 50 mg three times a day after meals, and hydrochlorothiazide 50 mg daily. However, the hypoglycaemic episodes did not subside after one month of this therapy due to steroid resistance. Rituximab therapy was given as 1 gm IV infusion was given along with methylprednisolone 125 mg intravenously as premedication. Within seven days the hypoglycaemic episodes decreased to one episode every three days. A second dose of rituximab 1 gm IV infusion was given 15 days after the first dose.

The insulin antibodies became normal, and serum insulin levels decreased from 24000 uU/ml to 200 uU/ml after three months of the second dose of rituximab [Tables 3A, 3B]. Freestyle libre glucose monitoring system showed no hypoglycaemic episodes after one month of the second dose. Prednisolone was tapered over three months. Side effects of steroids were persistent backache, weight gain, proximal myopathy, and facial puffiness. Osteoporosis was proved by a Dexa scan of the hip and spine. The backache improved after treatment with zoledronic acid and the other side effects regressed after steroids were withdrawn.

Case 5

A 73-year-old man was admitted with sudden onset of stiffness and loss of power in the right hand for 5 seconds, and a second such episode after 2 hours. He was hypertensive on amlodipine 10 mg daily. His pulse rate was 88/min regular; all peripheral pulses were palpable. His BP was 136/80 mm/hg. The systemic examination was normal, and there was no focal neurological deficit.

He consulted a neurologist who diagnosed him with transient ischemic attacks and started aspirin, clopidogrel, and atorvastatin. His Holter monitoring was within normal limits. The carotid Doppler showed atherosclerosis in both carotid arteries. MRI brain showed periventricular areas of chronic small vessel ischemic changes. His postprandial blood sugar was 329 mg/dl, but his Hba1c was 5.8% showing that there was transient hyperglycaemia for less than 3 months. Serial blood sugar monitoring revealed hypoglycaemic episodes of 50 mg/dl alternating with hyperglycaemic episodes of up to 300 mg/dl. He put on freestyle libre monitoring, which revealed that time in the target was 40%, 30% below target, and 30% above target.

In the hospital, glucose monitoring was done two hourly. One day 4 hours after breakfast, his blood sugar was 24 mg/dl, serum insulin was 7512 uU/ml, and serum c peptide was 18 pg/ml confirming hyperinsulinemic hypoglycaemia. Serum insulin antibodies were 140.34 units/ml (*n* <12). [Tables 2, 3A, 3B]

A diagnosis of IAS was made, and the patient started on prednisolone 40 mg daily along with metformin 500 mg × twice daily with a low carbohydrate high protein 1400 calories diabetic diet. Clopidogrel was stopped.

The hypoglycaemic attacks decreased within one week, but sugar was down to 60 mg/dl, 3-4 times a day. After one month of steroids, his hypoglycaemic attacks decreased to once in 3 days, relieved by oral glucose. There were no further symptomatic hypoglycaemic attacks after 6 weeks of 40 mg prednisolone. After tapering prednisolone over 6 months to 2.5 mg/day, serum insulin was >600 uU/ml, C-peptide of 5.15 ng/ml, Hba1c 5.15%, at a fasting blood sugar of 79 mg/dl. He was advised for immunosuppressive therapy but declined. He does not have symptomatic hypoglycaemia and is still on 2.5 mg of prednisolone/day prescribed by another endocrinologist.

Case 6

A 60-year-old man presented with recurrent episodes of sweating, tremors, dizziness, and palpitation in the early morning for the last 2 months, with blood sugar varying from 40 to 60 mg/dl during episodes, and the symptoms relieved by oral glucose. He had a history of COVID-19 (Covishield) vaccination 2 weeks before his symptoms started.

After admission, his blood sugar was monitored every 2 hours. He had several episodes of hypoglycaemia and hyperglycaemia between 12 midnight and 6 am with blood sugars ranging between 40 mg/dl and 290 mg/dl. When the blood sugar was 40 mg/dl,

his serum insulin was 17925 uU/ml, C-peptide of 23.87 ng/ml, and serum insulin autoantibodies >300 u/ml (n <12). [Tables 2, 3A, 3B] We made a diagnosis of IAS. The patient started on a 1600-calorie diabetic diet with 15 g of corn starch thrice daily mixed in soup and octreotide 50 mg subcutaneously thrice daily before meals. The patient continued to have hypoglycaemic attacks. Prednisolone was started at a dose of 60 mg daily. We put the patient on a freestyle libre glucose monitoring system.

After 1 month, his freestyle libre showed persisting episodes of hypoglycaemia going down to 50 mg/dl [Figure 1]. His was negative for hepatitis, infections, and pulmonary tuberculosis. He was given 1 gm of rituximab iv in 500 ccs normal saline at 25 ml/hour for 1 hour, 50 ml/hour for the next hour, and then 75/ml per hour, keeping track of vital parameters for allergic reactions or hypotension.

The hypoglycaemic episodes decreased with the first dose. However, the patient still developed one or two episodes of hypoglycaemia at night, with sugars going down to 60 mg/dl. In addition, the serum insulin levels had come down to 1404 uU/ml from 17950 uu/ml and insulin autoantibodies from 300 u/ml to 62 u/ml. Therefore, after 15 days, the second dose of 1 gm rituximab was also given.

Hypoglycaemic episodes decreased to one mild episode per day, easily corrected by oral glucose. [Figure 2] The patient had developed facial puffiness, and weight gain due to steroids. The patient developed shortness of breath and a high-grade fever. He was diagnosed to have *pneumocystis carnii* and cytomegalovirus infection which were treated with valganciclovir and trimethoprim/sulphamethoxazole for three weeks. The steroids were changed to hydrocortisone and tapered off in another 3 weeks.

Ethical aspects

The study was conducted following institutional ethics committee approval (Ethics Committee Indraprastha Apollo Hospital, IEC No.: IAH-BMR-068/09-23 dated 16 Sep 2023) in accordance with the declaration of Helsinki 1964. Written consent was obtained from all the patients.

Discussion

In 82% of cases, IAS is self-remitting, treated by the withdrawal of triggers and diet therapy. IAS refractory to diet therapy, should be treated with corticosteroids.[3] Prednisolone 30-60 mg is given for 4-6 weeks and then slowly tapered off. Steroid refractory IAS are challenging to manage and immunosuppression with Rituximab is the best treatment.[7-9] We started our patients on diet therapy, and steroids simultaneously. Novel treatment methods with rituximab were used in two patients resistant to steroids.

IAS is more common in people with a genetic predisposition positive for haplotypes HLA DR4-DRB1*0406, DRB1 0403, DRB10407.[3,10] Drugs or viral infections may trigger IAS or IAS can occur spontaneously. Triggers for IAS include drugs like methimazole, propylthiouracil, alpha lipoic acid, captopril, clopidogrel, pantoprazole, penicillamine, penicillin, isoniazid, imipenem, methionine, glutathione, mercaptans, hydralazine, and viral infections like mumps, rubella, measles, hepatitis C, chickenpox.[11,12] [Table 1] Possible triggers in our series were amoxicillin-clavulanic acid in Patient 1, aceclofenac in Patient 2, and clopidogrel in Patient 5. Patient 6 had received Covishield 2 weeks before the onset of hypoglycaemia [Tables 3A, 3B]. There is only 1 reported case of IAS developing one month after COVID-19 infection. SARS-CoV-2 infection or vaccination might induce insulin tolerance failure.[13] The prevalence of IAS is increasing, and this is partly due to the widespread use of dietary supplements containing α-lipoic acid.[2,3,9]

IAS may be associated with haematological diseases, such as multiple myeloma and monoclonal gammopathy, of unknown significance.[14] Patient 2 had polyclonal gammopathy.

Hypoglycaemia presents with symptoms ranging from mild to very severe and life-threatening[2,3,9] [Table 2]. Patients 1, 2, and 4 had severe life-threatening symptoms like loss of consciousness. Patient 5 had two episodes of transient ischemic attacks presenting stiffness and loss of power of the right hand for 5 seconds. Patients 3 and 6 had sweating and palpitations, tremors [Table 2].

IAS is associated with other autoimmune disorders,[2,3] but in our study, only patient 4 had primary hypothyroidism, the other five patients had no autoimmune disorder.

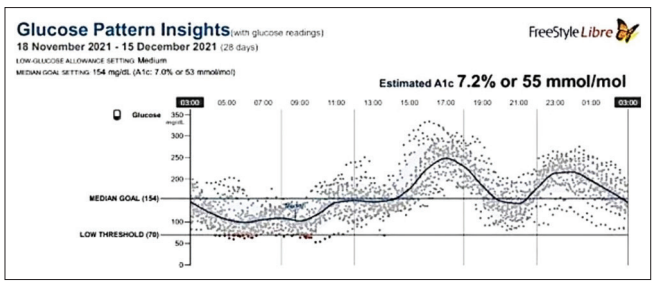

Figure 1: Freestyle libre glucose monitoring system readings in patient 6 after steroid therapy showing persistence of hypoglycaemic attacks in the morning and hyperglycaemia in the afternoon and night

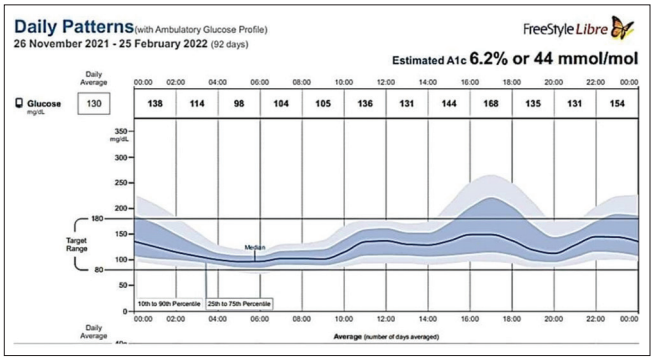

Figure 2: Freestyle libre glucose monitoring system readings in patient 6 showing normalization of hypoglycaemia but hyperglycaemia still persisting from 2 pm to 8 pm after two doses of rituximab therapy

IAS is the only known condition in which serum insulin levels are so high. Insulinoma patients do not have such high levels.[2,3,9] In autoimmune insulin syndrome due to insulin receptor antibodies, serum insulin, C-peptide, and proinsulin are increased but not as high as in IAS due to insulin antibodies. Also, 80% are females, and 80% have acanthosis nigricans in axillary, periocular, and perioral areas, and the groins, hyperandrogenism, enlarged ovaries, and high testosterone levels. They almost always have an associated autoimmune disorder like SLE or multiple myeloma. When the titre of insulin receptor antibodies is low, the insulin-mimetic action prevails, causing hypoglycaemia. When the titre of insulin receptor antibodies is high, insulin resistance is predominant, causing severe hyperglycaemia.[9,15,16]

Patient 1 had a hypoechoic lesion in the distal pancreas, probably an artifact because the histopathology showed normal pancreatic tissue. There were very high Insulin levels and high titres of insulin antibodies. Distal pancreatectomy reduced the number of beta cells, followed by spontaneous remission. However, a relapse of symptoms occurred after 3 years probably because amoxicillin intake triggered insulin autoantibodies. This patient was wrongly operated on for insulinoma. Exogenous insulin was ruled out as history did not suggest it, and C-peptide levels were not suppressed. We do not have facilities for sulphonyl urea assays in our country and there was no clue in the history to suggest it.

Treatment with complex carbohydrates in the form of corn starch and removing the triggering factors helps in treating hypoglycaemia.[17,18] Diazoxide and octreotide reduce insulin secretion and are useful in reducing hypoglycaemia.[3] IAS, which is refractory to diet therapy, should be treated with corticosteroids. Prednisolone 30-60 mg is given for 4-6 weeks and then slowly tapered off.[3,18] We started all our patients on diet and steroids. Patients 1,2, 3, and 5 showed improvement in symptoms and achieved remission, but patients 4 and 6 did not improve, requiring immunosuppression with Rituximab [Tables 2, 3A, 3B].

Patients need self-monitoring of blood glucose (SMBG) 2 hourly, with a glucometer or continuous glucose monitoring system (CGMS) when symptomatic. We used SMBG monitoring in all patients. However, in patients 4 and 6, we used a freestyle CGMS, which provided real-time blood sugar values, total time in hypoglycaemia, and total time in the range (TIR). Saxon DR achieved similar results with CGMS.[8] Low blood sugar values in CGMS were confirmed by glucometer or laboratory.

Options available for patients who are refractory to steroids are azathioprine,[2,3] cyclophosphamide,[2,3] mycophenolate mofetil,[19] Rituximab,[7,8,18,20] and plasmapheresis.[21] The best results were with rituximab.[7] Patients 4 and 6 were refractory to prednisolone, so we used rituximab, a monoclonal antibody against CD 20 on B lymphocytes. It is attached to CD 20 on B cells, making it susceptible to NK cells to phagocytose the abnormal antibody-producing B cells.[7,8,18] Rituximab 1 g was started with premedication using solumedrol, and the second dose of rituximab 1 g was given 14 days later. Remission was induced and no relapse occurred.[18]

Conclusion

IAS is one of the causes of endogenous hyperinsulinemic hypoglycaemia. The symptoms vary from mild palpitation and sweating to severe convulsions, impending death, and coma [Table 2]. Very high serum insulin with increased serum C-peptide and positive insulin antibodies are diagnostic of this disease. Although it is often self-remitting, steroids are necessary in severe cases. Immunosuppressives are used successfully in cases refractory to steroids. A careful history including recent infections, medications, and vaccinations provides vital clues in the evaluation and increased awareness of IAS will prevent unnecessary and costly investigations and surgery. Low CGMS values should be corroborated clinically and also with lab or glucometer values.

Acknowledgement

Faculty of Radiology and Biochemistry Departments, Indraprastha Apollo Hospitals.

Authors' contribution

All the authors deserve equal credit for this paper. They helped me in managing these cases, in data acquisition, research work, making tables and figures, and in preparing this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hirata Y, Ishizu H, Ouchi N. Insulin autoimmunity in a case of spontaneous hypoglycemia. J Jpn Diabetes Soc 1970;13:312–20.
2. Lin M, Chen Y, Ning J. Insulin autoimmune syndrome: A systematic review. Int J Endocrinol 2023;2023:1225676.
3. 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;13:963-78.
4. Dhaliwal KK, Bector G, Arora S, Singh A, Kalra S. An uncommon case of recurrent hypoglycemic episodes in a healthy non-diabetic male: Insulin autoimmune syndrome. Cureus 2023;15:e41183.
5. Patel M, Shah R, Ramteke-Jadhav S, Patil V, Patel SK, Lila A, *et al*. Management of insulin autoimmune hypoglycaemia: Single-centre experience from Western India with systematic review of world literature. Clin Endocrinol (Oxf) 2020;92:409-20.
6. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, *et al*. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009;94:709-28.
7. Church D, Cardoso L, Kay RG, Williams CL, Freudenthal B, Clarke C, *et al*. Assessment and management of anti-insulin autoantibodies in varying presentations of insulin autoimmune syndrome. J Clin Endocrinol Metab 2018;103:3845-55.
8. Saxon DR, McDermott MT, Michels AW. Novel management of insulin autoimmune syndrome with rituximab and continuous glucose monitoring. J Clin Endocrinol Metab 2016;101:1931–4.
9. Censi S, Mian C, Betterle C. Insulin autoimmune syndrome: From diagnosis to clinical management. Ann Transl Med 2018;6:335-3.

10. Uchigata Y, Kuwata S, Tsushima T, Tokunaga K, Miyamoto M, Tsuchikawa K, *et al*. Patients with Graves' disease who developed insulin autoimmune syndrome (Hirata disease) possess HLA-Bw62/Cw4/DR4 carrying DRB1*0406. J Clin Endocrinol Metab 1993;77:249-54.
11. Bodansky HJ, Grant PJ, Dean BM, McNally J, Bottazzo GF, Hambling MH, *et al*. Islet-cell antibodies and insulin autoantibodies in association with common viral infections. Lancet 1986;2:1351-3.
12. Zhang Y, Zhao T. Hypoglycemic coma due to insulin autoimmune syndrome induced by methimazole: A rare case report. Exp Ther Med 2014;8:1581-4.
13. Corona-Meraz FI, Quintero-Castillo BP, Hernández-Palma LA, Machado-Sulbaran AC. Long COVID-19 and insulin autoimmune syndrome: A case report. Clin Ther 2023;45:e187-92.
14. Lichtman MA, Balderman SR. Unusual manifestations of essential monoclonal gammopathy. II. Simulation of the insulin autoimmune syndrome. Rambam Maimonides Med J 2015;6:e0027.
15. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore) 2009;88:141–53.
16. Redmon JB, Nuttall FQ. Autoimmune hypoglycemia. Endocrinol Metab Clin North Am 1999;28:603–18.
17. Deguchi A, Okauchi Y, Suehara S, Mineo I. Insulin autoimmune syndrome in a health supplement user: The effectiveness of cornstarch therapy for treating hypoglycemia. Intern Med 2013;52:369-72.
18. Batra CM, Kumar K, Goyal M. Steroid-refractory insulin autoimmune syndrome treated with rituximab and continuous glucose monitoring. Cureus 2021;13:e16513.
19. Segal T, Webb E, Viner R, Pusey C, Wild G, Allgrove J, *et al*. Severe insulin resistance secondary to insulin antibodies: Successful treatment with the immunosuppressant MMF. Pediatr Diabetes 2008;9:250-4.
20. Kroemer TM, Erler A, Tsourdi E, Gruber M, Tselmin S, Julius U, *et al*. Immunoadsorption followed by rituximab as a definitive treatment for insulin autoimmune syndrome (Hirata Syndrome): A case report. Diabetes Care 2018;41:e23-4.
21. Yaturu S, DePrisco C, Lurie A. Severe autoimmune hypoglycemia with insulin antibodies necessitating plasmapheresis. Endocr Pract 2004;10:49-54.