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Case report

Insulin Autoimmune Syndrome: a rare case of hypoglycaemia resolving with immunosuppression.

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ABSTRACT

We report a case of a 58-year-old male presenting with confusion and hypoglycaemia. There had been no prior exposure to oral hypoglycaemic agents or insulin. He was found to have inappropriate endogenous hyperinsulinaemia. Insulinoma was excluded by detailed endocrine assessment. Insulin antibodies were positive in keeping with a diagnosis of insulin autoimmune syndrome (IAS). He was treated with prednisolone 5mg once daily and nutritional supplements leading to resolution of acute confusion and hypoglycaemic episodes.

The patient also had severe psoriasis and following discharge was treated with a variety of immunosuppressant therapies. This was associated with disappearance of insulin antibodies after twelve months of follow up. While it is possible that there was spontaneous resolution of insulin antibodies, we speculate that his prednisolone and immunosuppressant therapy may have suppressed insulin antibody production.

There are several well recognised associations with IAS and autoimmune conditions, including Grave's disease, systemic lupus erythematous and rheumatoid arthritis. To our knowledge this is the first reported case of insulin autoimmune syndrome, resolving with immunosuppressant treatment of psoriasis.

CASE REPORT

A 58-year-old male presented to the emergency department (ED) with new onset confusion. He had a history of learning difficulties and his family had found him to be confused and disorientated. The patient gave a one day history of feeling unwell and reported unsteadiness. He had no recent weight loss and his appetite had been normal. He was brought to the emergency department via ambulance having been treated for hypoglycaemia (capillary blood glucose (CBG) 1.9 mmol/L) with glucagon and intravenous glucose by the paramedic team. On arrival in ED, his CBG was 11.9 mmol/L. He was admitted for further investigation and monitoring. Past medical history included psoriasis, epilepsy and stroke. Medications at presentation were acitretin, coal tar solution 5%, oilatum, sodium valproate, carbamazepine, simvastatin and clopidogrel.

Capillary blood glucose was closely monitored during admission and he had recurrent episodes of late night and early morning hypoglycaemia, treated with a variety of oral glucose preparations and long acting carbohydrates.

During an episode of hypoglycaemia, bloods were sent for laboratory analysis revealing plasma glucose 2.6 mmol/L, serum insulin >1000 mU/L (reference range 2.6 -24.9 mU/l), serum C-peptide 17.4 ug/L (reference range 1.4 -4.4 ug/l). Sulphonylurea use was excluded by a negative drug screen. Adrenal insufficiency was excluded following a short Synacthen test (serum cortisol T0= 408 nmol/l and T30 = 1008 nmol/l).

He proceeded to a formal 72 hour fast to exclude endogenous hyperinsulinaemia. The fast was stopped at 23 hours (see Table 1) as CBG fell to 2.3 mmol/L and he was symptomatic with sweating and dizziness. Hypoglycaemia was confirmed on plasma glucose testing and insulin and C-peptide remained significantly and inappropriately elevated.

Table 1

Plasma glucose, 3-OH butyrate, insulin and C-peptide data during 72 hour fast.

	Time of blood test			
	18.30	06.20	09.10	15.45
Glucose (mmol/L)		3.5		2.3
3-OH butyrate (mmol/L)			0.01	0.32
Insulin (mU/L)	>1000	>1000	>1000	>1000
C-peptide (ug/L)	17.0	20.7	*	19.6

(*missing data)

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TABLE 2

Serum insulin levels undertaken during calcium stimulated selective venous sampling of localisation study

Time (seconds)	Gastroduodenal insulin (mU/L)	Proximal splenic insulin (mU/L)	Distal splenic insulin (mU/L)	Hepatic artery insulin (mU/L)	Superior mesenteric artery insulin (mU/L)
0	6950	7150	7250	6850	*
30	7050	7000	7500	7100	7550
60	6700	7950	7050	6750	7500
90	6850	7150	7300	6700	7450
120	6900	6900	7700	6950	7550

(*missing data)

His 72 hour fast results were in keeping with endogenous hyperinsulinemia, potentially arising from an insulinoma. CT scanning of the abdomen and pelvis showed subtle changes in a small area at the head of the pancreas. The case was discussed at a Multi-disciplinary meeting with an agreed plan for localisation studies with calcium stimulation testing and endoscopic ultrasound (EUS) of pancreas. EUS was undertaken and identified a poorly circumscribed hyperechoic abnormality in the tail of the pancreas measuring 13x11mm. Fine needle aspiration showed benign pancreatic acini cells only, with no features of insulinoma.

A calcium stimulated localisation study with venous sampling was non-localising with no focal area of increased pancreatic insulin production (Table 2). Pancreatic hormones were also normal, again making pancreatogenous hypoglycaemia unlikely (Table 3).

TABLE 3

Fasting gut hormone screen

Hormone	Level
Gastrin	<30 ng/L
Pancreatic polypeptide	75 ng/L
Somatostatin	18 ng/L
Total chromogranin A	14 U/L
Vasoactive peptide	34 ng/L
Neurokinin A	11 ng/L

Initial insulin assay measurements were initially undertaken at the Regional Endocrinology laboratory using the Roche electrochemiluminescence (ECLIA) insulin immunoassay, which is specific for human insulin. Samples were also analysed separately using the alternative Mercodia enzyme-linked immunosorbent (ELISA) iso-insulin assay at an external laboratory, which has 55% cross reactivity with proinsulin and several other exogenous insulin treatments. Both methods are standardised to 1st International Reference Preparation 66/304 for human insulin.

Inappropriately elevated insulin concentrations were also confirmed using the ELISA method at 124 pmol/L (Reference range <30 pmol/l) with proinsulin concentrations at 31 pmol/L (Reference range <10 pmol/l) while the patient was hypoglycaemic at 2.3 mmol/l.

In view of massively elevated insulin concentrations and positive insulin antibodies (confirmed on two occasions), Insulin Autoimmune Syndrome was considered the likely diagnosis. Due to recurrent persistent and disabling hypoglycaemia, empirical treatment with prednisolone 5mg daily was commenced alongside nutritional support with frequent small meals, particularly in the evening period. There was a good symptomatic and biochemical response to treatment, and he was able to return home with the help of his family who supported regular CBG monitoring.

LONG-TERM FOLLOW UP

After six weeks at review there was complete resolution of hypoglycaemic episodes. Non-fasting insulin concentrations measured at the local laboratory after 21 months had fallen to 41.5 mU/L. Three years from diagnosis insulin antibodies were no longer detected on blood sampling and insulin concentrations had fallen to 34 mU/L, in keeping with long-term remission.

Interestingly, this patient has severe psoriasis which had failed to respond to multiple systemic medications. His psoriasis became increasingly difficult to control from 4 months prior to presentation requiring the use of intermittent potent topical steroids and Acitretin, a synthetic aromatic analogue of retinoic acid. He started immunosuppressants eight months after presentation namely Methotrexate (April 2014 - December 2015), Ciclosporin (December 15 – June 16), Adalimumab (June 16 - November 16) and Ustekinumab (November 16 – present). Insulin levels over time are plotted in Figure 1.

DISCUSSION

We present an interesting case of hypoglycaemia arising from apparent insulin antibody mediated hypoglycaemia, which was treated successfully with prednisolone and nutritional supplements leading to resolution of symptoms and hypoglycaemia. Significantly, the patient was treated with a variety of immunosuppressant therapy for management of psoriasis, which was associated with disappearance of insulin antibodies after seventeen months of follow up. While it is possible that there was spontaneous resolution of insulin antibodies, his prednisolone and immunosuppressant

therapy appear to have reduced insulin antibody production as evidenced by a reduction in measured serum insulin concentrations and disappearance of insulin antibodies.

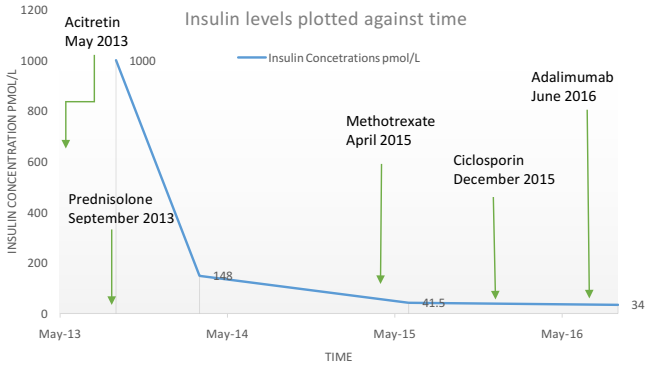

Fig 1. Insulin concentrations (mU/L) with time and immunosuppressant medication start times

There are several well recognised associations with insulin autoimmune syndrome (IAS) and autoimmune conditions, including Grave's disease, systemic lupus erythematous and rheumatoid arthritis. To our knowledge this is the first reported case of insulin autoimmune syndrome with resolution of markers of autoimmunity treated with immunosuppressant treatment of psoriasis.

Insulin autoimmune syndrome (IAS), or Hirata's Disease, was first described in 1972 in a Japanese patient who presented with hypoglycaemia. It is now recognised as the 3rd most common cause of hypoglycaemia in Asian patients. This follows insulinoma and non-pancreatic neoplasia as the first and second most common aetiologies respectively [1]. IAS has been increasingly recognised in Caucasian patients with several cases reported. It has a higher incidence in people who are HLA-DR4 positive or with other autoimmune conditions[2]. There have been published cases of IAS in patients with co-existent hyperthyroidism, systemic lupus erythematous and systemic sclerosis but to our knowledge none with psoriasis[3].

Triggers of IAS are drugs particularly those containing a sulfhydryl group[4] and exogenous insulin. This patient was never exposed to exogenous insulin, however he was taking clopidogrel, which is known to contain a sulfhydryl group, for a previous stroke,[5]. As clopidogrel was started two years prior to presentation it was not felt to be the trigger in this case and he remains on treatment. Virus exposure and myeloma are also potential causes of IAS, and these were excluded early in his assessment[1,6].

A variety of treatments of IAS have been reported in the literature, most commonly watchful waiting or removing the triggering medication. In most of cases stopping the culprit medication will induce spontaneous remission. Other treatments include high dose prednisolone (60mg once a day), azathioprine and 6-mercaptopurine[7]. Recently Rituximab was successfully used to treat refractory hypoglycaemia secondary to insulin autoantibodies in the absence of exogenous insulin being used[7]. Plasmapheresis has also been used in cases of refractory hypoglycaemia and in an extreme case, pancreatic surgery when immunosuppression was inappropriate due to sepsis[8].

An additional challenge in this case was that the patient had a learning disability and was unable to communicate his symptoms of hypoglycaemia or manage them independently. Empirical treatment with 5mg prednisolone once a day was used to alleviate hypoglycaemia symptoms. He responded well to treatment, which also included dietary adjustment with complete resolution of hypoglycaemia within weeks.

Seven months after insulin antibodies were identified he was commenced on further immunosuppressant medication under the supervision of his dermatologist. It is difficult to conclusively determine, which if any, of these treatments reduced insulin antibody generation in addition to impact of his prior course of oral corticosteroids. While it is also possible that spontaneous resolution of IAS may have occurred, he seems to have made good progress on treatment and his condition remains in remission with a reduction in measured serum insulin concentrations and disappearance of insulin antibodies.

In conclusion, insulin autoimmune syndrome is a rare but important differential diagnosis in individuals presenting with hypoglycaemia. This condition should be considered in patients with inappropriate endogenous hyperinsulinaemia in whom insulinoma has been excluded. Other factors including previous insulin treatment, exposure to sulfhydryl containing medications and extremely high serum insulin levels may point towards the diagnosis.

REFERENCES

1. Ismail AA. The insulin autoimmune syndrome (IAS) as a cause of hypoglycaemia: an update on the pathophysiology, biochemical investigations and diagnosis. *Clin Chem Lab Med*. 2016; **54(11)**: 1715–24.
2. Cavaco B, Uchigata Y, Porto T, Amparo-Santos M, Sobrinho L, Leite V. Hypoglycaemia due to insulin autoimmune syndrome: report of two cases with characterisation of HLA alleles and insulin autoantibodies. *Eur J Endocrinol*. 2001; **145(3)**:311-6.
3. Wang YL, Yao PW, Zhang XT, Luo ZZ, Wu PQ, Xiao F. Insulin autoimmune syndrome: 73 Cases of Clinical Analysis. *Chin Med J*. 2015 **128(17)**:2408-9.
4. Jain N, Savani M, Agarwal M, Kadaria D. Methimazole-induced insulin autoimmune syndrome. *Ther Adv Endocrinol Metab*. 2016; **7(4)**:178-81.
5. Wijeyeratne YD, Heptinstall S. Anti-platelet therapy: ADP receptor antagonists. *Br J Clin Pharmacol*. 2011; **72(4):**647-57.
6. Waldron-Lynch F, Inzucchi SE, Menard L, Tai N, Preston-Hurlburt P, Hui P, *et al*. Relapsing and remitting severe hypoglycemia due to a monoclonal anti-insulin antibody heralding a case of multiple myeloma. *J Clin Endocrinol Metab*. 2012; **97(12)**:4317-23.
7. Saxon DR, McDermott MT, Michels AW. Novel management of Insulin Autoimmune Syndrome with Rituximab and Continuous Glucose Monitoring. *J Clin Endocrinol Metab*. 2016; **101(5)**:1931-4.
8. Moreira RO, Lima GA, Peixoto PC, Farias ML, Vaisman M. Insulin autoimmune syndrome: case report. *Sao Paulo Med J*. 2004; **122(4)**:178-80.