CASE REPORT

Postprandial hyperinsulinaemic hypoglycaemia and type 1 diabetes mellitus

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A patient with severe postprandial hyperinsulinaemic hypoglycaemia (PPHH) for 4 years developed type 1 diabetes mellitus. She had no insulin or insulin receptor antibodies but was positive for islet cell and glutamic acid decarboxylase (GAD) antibodies. PPHH prior to the onset of type 1 diabetes mellitus has not been previously described and may be a prodrome of type 1 diabetes mellitus.

Type 1 diabetes mellitus (DM) is caused by the loss of insulin-secreting capacity due to selective autoimmune destruction of the pancreatic beta cells. Antibodies to the cytoplasm of islet cells, glutamic acid decarboxylase (GAD), insulin and tyrosine phosphatase-like protein (IA-2 or IA-2 β), which appear before the clinical onset of DM, are markers of the autoimmune process.¹ These autoantibodies can appear many months or years before the onset of clinical disease. Hypoglycaemia in type 1 DM is well recognised and is typically the result of the interaction between excess insulin administration and a compromised glucose counter-regulatory hormonal response.

Postprandial hyperinsulinaemic hypoglycaemia (PPHH) refers to the development of hypoglycaemia within a few hours of meal ingestion. It is associated with inappropriate insulin secretion in response to the meal. However, the precise physiological mechanisms that lead to unregulated insulin secretion in response to a meal are not clear. The occurrence of hypoglycaemia prior to the onset of type 1 DM is rare and, more specifically, PPHH prior to the onset of DM has not been previously described.

CASE HISTORY

The patient was born at term by normal vaginal delivery following an uneventful pregnancy. Her birth weight was 3.4 kg. She had mild jaundice but no other perinatal problems. She developed normally until 3 years of age, but subsequently her development slowed. At age 7 years, she was diagnosed with primary hypothyroidism and commenced on thyroxine. Thyroid autoantibodies were not measured at the time of diagnosis. At 8 years of age, she was noted to have an increased appetite and had developed mood swings, becoming suddenly irritable and irrational. She was described as being tired and having poor concentration. These symptoms would improve after food. In addition, she was difficult to wake in the morning and complained of morning headaches, which also improved with food. There was no family history of DM or other autoimmune disease.

At 10 years of age she started having seizures. She was noted to have myoclonic jerking of the right hand, and then collapsed and was unresponsive. She recovered after 5–7 min, but complained of a headache. She was taken to an emergency department and her laboratory blood glucose concentration was 3.1 mmol/l several hours after the seizure and after having had

food. She continued to have episodes of confusion and shaking of her limbs, generally occurring 1–2 h after meals. These episodes improved with food. An EEG demonstrated generalised epileptiform changes, especially over the right fronto-temporal region. An MRI of the brain was normal.

The patient was referred to Great Ormond Street Children's Hospital NHS Trust for further investigations. Her 24-h blood glucose and cortisol profiles were normal as was a standard dose Synacthen test. She was able to fast for 18 h without developing hypoglycaemia. During the fast she had appropriate suppression of insulin concentrations and generated an appropriate non-esterified fatty acid and total ketone body response. She then proceeded to a prolonged oral glucose tolerance test (OGTT) and developed severe symptomatic hypoglycaemia (collapse and unconsciousness; laboratory blood glucose concentration 1.8 mmol/l) at 3 h into the test. An exaggerated insulin (and C-peptide) response was demonstrated throughout the OGTT and at the time of hypoglycaemia insulin concentration was 31.6 mU/l (table 1). Her non-esterified fatty acid and total ketone body response was suppressed (as a result of the hyperinsulinaemia). The serum ammonia, lactate, pyruvate, plasma amino acids, total and free carnitines and urine organic acids were normal at the time of hypoglycaemia. She generated appropriate increases in serum cortisol, growth hormone and glucagon counter-regulatory hormonal responses. Hence severe PPHH was diagnosed and this patient was advised to have small, frequent feeds to prevent surges in insulin secretion.

The patient was then reviewed at 11.3 years of age and reported continuing symptoms of PPHH, especially after any large meal. At 11.6 years of age, she presented to her local hospital with a 24-h history of polyuria, polydipsia and home capillary blood glucose measurements of >20 mmol/l. She was noted to be hyperglycaemic (blood glucose 11.2 mmol/l) with

Table 1 Results of the oral glucose tolerance test (OGTT)

Time (min)	Glucose (mmol/l)	Insulin (mU/l)	C-peptide (pmol/l)
–30	4.2	16.2	265.6
0	4.3	14.4	NM
30	9.8	50.8	790.4
60	10	82.7	NM
90	7.5	107	2190.4
120	5	65.6	1276.4
150	4.9	56.2	NM
180	1.8	31.6	NM

NM, not measured.

The patient became unconscious at 180 min into the OGTT when her blood glucose concentration was 1.8 mmol/l. She required resuscitation with intravenous glucose to correct her hypoglycaemia. The serum insulin level was inappropriately elevated when the blood glucose level was 1.8 mmol/l.

Abbreviations: DM, diabetes mellitus; GAD, glutamic acid decarboxylase; IAS, insulin autoimmune syndrome; OGTT, oral glucose tolerance test; PPHH, postprandial hyperinsulinaemic hypoglycaemia

glycosuria and ketonuria. She was treated with short acting insulin and discharged home. Investigations confirmed the presence of islet cell, GAD and thyroid peroxidase antibodies. Her insulin IgG antibodies were within the reference range (<5 mU/l) and she had no insulin receptor antibodies. She was therefore diagnosed with type 1 DM and commenced on a basal bolus insulin regimen.

DISCUSSION

The mechanism of PPHH is unclear in this patient. The hypoglycaemia is not associated with fasting as she was able to fast for 18 h with a normal blood glucose concentration at the end of the fast. The hypoglycaemia was only elicited after a prolonged OGTT. PPHH is extremely rare in childhood. The most common cause is due to the "dumping" syndrome in infants who have undergone gastro-oesophageal surgery.² Nearly all other causes of PPHH have been reported in adults. PPHH has been reported in the insulin autoimmune syndrome (IAS; mostly in adults) which is characterised by the presence of insulin-binding autoantibodies in subjects who have not been previously exposed to exogenous insulin.³ In IAS there is a high serum concentration of total immunoreactive insulin, and insulin autoantibodies are present in high titres.³ This syndrome classically presents with hypoglycaemia several hours after a meal. Autoantibodies against endogenous insulin bind the hormone which is released later after the meal causing PPHH. The pathological histological findings in the pancreas in these patients is one of islet hyperplasia without evidence of inflammation, indicating that the condition is distinct from type 1 DM. The course of the autoimmune insulin syndrome is usually favourable, with spontaneous diminution in the levels of anti-insulin antibodies. The PPHH in our patient is not typical of patients with IAS, as her insulin antibodies were present in low titres and her fasting serum insulin was only slightly raised.

A syndrome of autosomal dominant PPHH with onset in adolescence to adulthood and linked to a mutation (Arg1174Gln) in the insulin receptor kinase gene has been reported.⁴ In these patients, a prolonged (5 h) OGTT demonstrates marked PPHH with clamp studies demonstrating reduced insulin sensitivity and clearance of serum insulin in affected family members compared with control subjects. In our patient, sequencing of the insulin receptor gene failed to detect any mutations. A syndrome of "non-insulinoma pancreatogenous" PPHH has also been recognised in adults.⁵ These patients demonstrate neuroglycopenic episodes from hypoglycaemia within 4 h of meal ingestion and have negative 72-h fasts.

However, none of the above causes can explain the PPHH observed in our patient. It is possible that the PPHH observed in

this patient is another autoimmune-mediated phenomenon. Although the precise cause of the PPHH is unclear, the clinical history may be analogous to that of patients with another autoimmune disease, namely Hashimoto's thyroiditis. In the early stages of Hashimoto's thyroiditis there is immune-mediated destruction of the thyroid gland (characterised by lymphocytic infiltration), which at first leads to hyperthyroidism. As the immune process continues there is continued destruction of the thyroid follicles with subsequent development of hypothyroidism. Hence in our patient the presumed autoimmune process might at first lead to unregulated insulin secretion, especially in response to meal ingestion. As the immune-mediated destruction continues there is a progressive decline in functional pancreatic β -cell mass, ultimately leading to type 1 DM.

In summary, this patient had severe PPHH for 4 years and then acutely developed type 1 DM. Her hypoglycaemia was not related to fasting or provocation (such as exercise or protein sensitivity). She had no insulin or insulin receptor antibodies but was positive for islet cell and GAD antibodies. Although the precise mechanism of PPHH in this patient is unclear, this case suggests that PPHH may be another prodrome of type 1 DM and that a prolonged OGTT may elicit some forms of PPHH.

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