CASE REPORT

Type 2 diabetes presenting with hyperglycaemic hyperosmolar state in an adolescent renal transplant patient

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SUMMARY

Hyperglycaemic hyperosmolar state (HHS) is a life-threatening condition rarely seen in paediatrics. It is becoming increasingly recognised with the growing incidence of childhood type 2 diabetes mellitus (T2DM). We present a 16-year-old boy with Bardet-Biedl syndrome, with comorbidities including chronic renal impairment requiring renal transplant, isolated growth hormone (GH) deficiency and obesity, who presented on routine follow-up with new onset T2DM and in HHS. Investigations revealed hyperglycaemia (45.7 mmol/L), ketones of 0.1 mmol/L, pH 7.38 and osmolality 311 mOsmol/kg. After acute management with fluid resuscitation and intravenous insulin, he is now stable on metformin. He has lost weight, renal function is stable and he has stopped GH therapy. We discuss the dilemmas encountered in his long-term management due to his renal transplant and comorbidities, and whether or not, given his significant T2DM risk, this case was preventable or predictable.

BACKGROUND

Hyperglycaemic hyperosmolar state (HHS) was previously thought to be a rare presentation of type 2 diabetes mellitus (T2DM) in children, but reported cases are on the rise. This is likely due to the increased prevalence of both T2DM and obesity in the paediatric population. Between 2001 and 2008, 65 cases of paediatric HHS were reported,¹ but the true incidence of this condition is still not known. Bardet-Biedl syndrome (BBS) is a rare heterogeneous autosomal recessive disorder affecting ciliary function. It has an estimated incidence of 1:160 000 in European populations² and the abnormal ciliary function has wide reaching effects on multiple organ systems. There is a wide range of clinical variability, but common features include retinitis pigmentosa, renal tract abnormalities (10% develop end-stage renal failure), developmental delay, polydactyly and hypogonadotrophic hypogonadism. It is also associated with obesity (72–92% of cases), hypercholesterolaemia and many children develop T2DM (6–48%).² We describe a rare case of a child with BBS, presenting with HHS, and the issues that were encountered in his management due to his multiple comorbidities and renal replacement therapy. In addition, this patient had multiple risk factors for T2DM—a predisposing syndrome, obesity, family history of T2DM, a high-risk ethnic background and treatment with steroids, tacrolimus and growth hormone (GH). In complex cases such

as this, especially when diabetogenic medications are prescribed, significant T2DM risk accumulates and the risk-benefit balance for prescribing such medication must be re-evaluated. Likewise, screening such patients for diabetes is essential to ensure early treatment and hence prevent unnecessary morbidity and mortality due to damaging a precious transplanted kidney, or the onset of HHS.

CASE PRESENTATION

A 16-year-old boy with BBS presented with an incidental finding of high blood glucose level on routine screening at a renal outpatient clinic. See [table 1](#) for his full case history. Of note, he was on immunosuppression therapies, and had been started on GH treatment from the age of 9 years. He had had a normal oral glucose tolerance test (OGTT) 18 months prior to presentation.

On presentation, he reported only a history of polydipsia in recent weeks, for which he had been drinking large quantities of sugary drinks. On examination, he was overweight (body mass index (BMI): 30.3 kg/m²; BMI SDS: 2.62), and tachycardic with a heart rate of 100 bpm but normal capillary refill and blood pressure of 121/69. Initial blood test results are shown in [table 2](#).

TREATMENT

Rehydration is the mainstay of initial treatment in HHS. HHS patients can be significantly more volume depleted than they appear. Our patient looked well, was mildly tachycardic with moist mucus membranes and was passing urine. His renal function however was deranged, and with the background of renal failure, it was decided to exercise caution with his fluid resuscitation. He was therefore initially managed with fluid resuscitation of normal saline 10 mL/kg over 1 h. This was followed by replacement of his estimated fluid deficit of 5% (with a plan to review this as necessary) over 48 h, plus maintenance fluids intravenously. He was admitted to the paediatric high dependency unit and started on an intravenous insulin sliding scale, initially running at 0.05 units/kg/h and weaned according to response. Once blood glucose and osmolality readings had improved, he was changed to subcutaneous insulin. He remained otherwise well and was discharged home on twice daily biphasic isophane insulin.

OUTCOME AND FOLLOW-UP

In the 12 months since his presentation, his glycaated haemoglobin (HbA1c) has improved from

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Table 1 Case history

Feature	Patient
Age	16 years
Medical history	BBS Renal impairment since birth—current GFR: 22 mL/min/1.73 m ² Renal transplant 1 year prior to presentation Isolated growth hormone deficiency Obesity Hypogonadism with micropenis Learning difficulties
Drug history	Tacrolimus: 1.5 mg mane and 2 mg nocte Prednisolone: 5 mg on alternate days Growth hormone: 1.8 mg alternating with 1.9 mg subcutaneously daily
Family history	T2DM: father and brother
Ethnicity	South Asian

BBS, Bardet-Biedl syndrome; GFR, glomerular filtration rate; T2DM, type 2 diabetes mellitus.

12.1% to 6.4%. Following initial twice daily treatment, he was changed to daily glargine monotherapy. Eight months after diagnosis, allowing time for an initial improvement in HbA1c using insulin, he was switched to long-term metformin only. GH treatment has been discontinued—there were concerns about the possible link between GH therapy and T2DM, particularly in such a high-risk patient. Following risk-benefit analysis, the family felt they were happy with his height outcome, and in discussion with the endocrine team, GH treatment was stopped.

DISCUSSION

Children with BBS have a tendency to develop metabolic syndrome and insulin resistance. They are often obese and it is thought the underlying ciliary defect leads to problems with appetite regulation, through an unknown mechanism. Forsythe

Table 2 Patient's blood test results on presentation

Test	Result	Normal range
Blood gas		
Glucose, mmol/L	45.7	3.0–5.5
Ketones, mmol/L	0.1	<0.6
pH	7.38	7.35–7.45
BE, mmol/L	−4.0	−2 to 2
Osmolarity, mOsmol/kg	311	278–295
Fluid status		
Corrected Na ⁺ , mmol/L	136	135–145
K ⁺ , mmol/L	4.5	3.5–5
Cl [−] , mmol/L	92	95–105
HCO ₃ [−] , mmol/L	19.9	22–30
Creatinine, μmol/L	166	40–96
	(Baseline creatinine for patient 108–133)	
Urea, mmol/L	10.4	3.0–7.5
	(Baseline urea for patient within normal range)	
Diabetic work up		
HbA1c, Per cent	12.1	4–6
mmol/mol	109	20–40
C peptide, nmol/L	1.15	0.27–1.28
GAD antibodies, IU/L	Negative	0–5
Islet cell antibodies	Negative	NA

BE, base excess; GAD, glutamic acid decarboxylase; HbA1c, glycated haemoglobin.

and Beales² recommended that children with BBS should be assessed for signs or symptoms of T2DM, including an OGTT on presentation if there is any suspicion of diabetes; however, there are no data on the requirement for further testing as the child matures. Owing to the rarity of the condition, there is no guidance on the timing or frequency of such testing.

The insidious onset of polyuria and polydipsia in HHS can go relatively unrecognised, as the worsening symptoms of diabetic ketoacidosis are not present; therefore, patients often present with significantly worse dehydration and electrolyte disturbances. Paediatric HHS has a high mortality rate, estimated at 37%; in stark contrast to the adult population (15%) where mortality rates have fallen dramatically due to improved management.¹ A recent case series reported deaths were largely due to multiorgan failure (73%). Other causes of mortality include pulmonary embolus (6.1%), hypokalaemia (4.6%) and cerebral oedema (1.5%).¹ Obese patients are likely to have a higher mortality rate as the degree of fluid loss can be difficult to assess clinically due to the body habitus. It is therefore fortuitous that our patient's hyperglycaemia was identified early, having been picked up initially by glycosuria at his routine renal follow-up. It is worth considering if this particular case was in any way more predictable or if he should have had more regular screening for the development of T2DM. This child had multiple risk factors for diabetes—a predisposing syndrome; obesity; a high-risk ethnic background; he was on steroids and tacrolimus, as well as GH replacement. There was a strong family history of T2DM. His reduced renal function increased the risk of presenting with HHS, rather than a more insidious T2DM.

Most children presenting with HHS require insulin for a period of stabilisation; they can then switch to oral hypoglycaemic agents alongside weight loss strategies such as lifestyle changes and diet control. ISPAD guidelines recommend metformin as first-line oral antidiabetic agent for T2DM.³ Management of T2DM on a background of renal transplant is more complex. Metformin carries a risk of lactic acidosis, and guidelines for its use in renal transplant patients are currently not available.⁴ Equally, other antidiabetic options have more commonly experienced side effects, as well as having less evidence base in children.

A more common phenomenon to consider is post-transplant diabetes mellitus (PTDM), which occurs in 2–35% of children postrenal transplant.⁵ It occurs largely due to the diabetogenic effects of the immunosuppressants, especially tacrolimus and corticosteroids, with the risk of this outweighed by the need to reduce graft rejection. Poor glucose control is associated with reduced patient survival, graft survival and function, and therefore a change to a less diabetogenic agent such as ciclosporin may need to be considered.⁶ Most research in PTDM focuses on adult cases and optimal choice of treatment for PTDM is still a topic under debate as efficacy of different antihyperglycaemics has not been evaluated.⁶

The role of GH in this case is controversial. While a link between T2DM is known in acromegaly,⁷ the effects of excess GH on glucose metabolism are complex and there is no evidence that therapeutic GH can induce T2DM. In this child's case, benefits of ongoing GH were felt to be minimal and the decision was made to stop the GH.

In summary, T2DM is increasingly common in the paediatric population. Clinicians should be aware of patients with multiple T2DM risk factors and the risk of diabetogenic medications, and should maintain a low threshold for diabetes screening, particularly in children with syndromes or conditions which predispose to diabetes such as BBS. This is particularly important in those patients with renal transplants, who are both at increased risk of diabetes and where poor glycaemic control could damage the child's

precious kidney. HHS in children and young people remains a rare syndrome but with the rise in T2DM in paediatrics, and the high mortality of HHS, it is an important diagnosis. Increased vigilance for such cases as this may make deaths preventable.

Learning points

- ▶ Hyperglycaemic hyperosmolar state is an increasingly common presentation of type 2 diabetes in paediatric patients.
- ▶ Clinicians should be aware of the potential diabetogenic effects of medications they prescribe, particularly immunosuppressants.
- ▶ Children with Bardet-Biedl syndrome are predisposed to type 2 diabetes mellitus and care should be exercised in managing these patients to minimise risk factors for hyperglycaemia and insulin resistance, and to screen for diabetes.
- ▶ Optimal management of glycaemic control in children with a renal transplant is uncertain but vigilance and careful consideration of treatment can preserve renal function.

Contributors The patient is under the long-term care of TM. FRH drafted the initial draft of the manuscript and all authors contributed to the editing and reviewing of the manuscript.

Competing interests None.

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