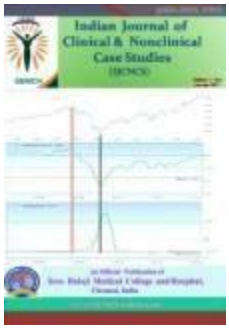

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TYPE 2 DIABETES PRESENTING WITH HYPERGLYCAEMIC HYPEROSMOLAR STATE IN AN ADOLESCENT RENAL TRANSPLANT PATIENT

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Abstract

A 16-year-old boy with BBS was on immunosuppression therapies from the age of 9 years had a normal oral glucose tolerance test (OGTT) 18 months prior to presentation. He had presented with an incidental finding of high blood glucose level on routine screening at a renal outpatient clinic. He reported only a history of polydipsia, for which he had been drinking large quantities of sugary drinks. On examination, we found him to be overweight (body mass index (BMI): 30.3 kg/m^2; BMI SDS: 2.62), and the patient exhibited mild tachycardic with a heart rate of 100 bpm but normal capillary refill and blood pressure of 121/69 with moist mucus membranes and was passing urine. His renal function was deranged. The patient was initially administered with normal saline 10 mL/kg followed by replacement of his estimated fluid deficit of 5% over 48 h, plus maintenance fluids intravenously. The patient was initially administrated paediatric unit 0.05 units/kg/h insulin and reduced depending on the response. Once blood glucose and osmolarity readings had improved, the patient was changed to subcutaneous insulin and was discharged home on twice daily biphasic isophane insulin. In the 12 months since his presentation, his glycatedhaemoglobin (HbA1c) has improved from 12.1% to 6.4%. Following initial twice daily treatment, he was changed to daily glarginemonotherapy. Eight months after diagnosis, allowing time for an initial improvement in HbA1c using insulin, the patient 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.

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

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INTRODUCTION:

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[1]. Between 2001 and 2008, 65 cases of paediatric HHS were reported, but the true incidence of this condition is still not known. Bardet –Biedl syndrome is a disorder that affects the ciliary function. It has an estimated incidence of 1:160 000 in European populations[2] 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%). 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.

Table 1

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

Feature	**Patient**
Age	16 years
Medical history	BBS Renal impairment since birth—current GFR: 22 mL/min/1.73 m2 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

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/m^2; 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.

Table 2

Patient's blood test results on presentation BE, base excess; GAD, glutamic acid decarboxylase; HbA1c, glycatedhaemoglobin.

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 (Baseline creatinine for patient 108–133)	40–96
Urea, mmol/L	10.4	3.0–7.5
Test	**Result**	**Normal range**
	(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

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. The patient was initially administered with normal saline 10 mL/kg 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. The patient was admitted to the paediatric unit 0.05 units/kg/h insulin was administrated initially and reduced depending on the response. Once blood glucose and osmolarity 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 glycatedhaemoglobin (HbA1c) has improved from 12.1% to 6.4%. Following initial twice daily treatment, he was changed to daily glarginemonotherapy. 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

Metabolic syndrome and insulin resistance may develop in children with BBS. They are often obese and it is thought the underlying ciliary defect leads to problems with appetite regulation, through an unknown mechanism. Forsythe and Beales 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. The patient's hyperglycaemia was detected early while he was initially having glycosuria 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.

Children with HHS require insulin treatment initially and they may be advised to use oral hypoglycaemic agents along with diet control, life style changes and exercise. ISPAD guidelines recommend metformin as first-line oral antidiabetic agent for T2DM.3 Management complex. Metformin carries a risk of lactic acidosis, and guidelines for its use in renal transplant patients are currently not available4. 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 be needed though the efficacy of antihyperglycaemics desired to be assessed for T2DM on a background of renal transplant is more.

The role of GH in this case is controversial. In this child's case, the benefits of ongoing GH treatment were felt to be minimal and hence the decision was discontinued. Whether or not that the therapeutic GH or excess GH can affect glucose metabolism and induce T2DM needs to be further investigated.

In conclusion, T2DM is found to be 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 is a rare syndrome and exhibit mortality and there is a tremendous increase in the incidence of T2DM in paediatrics and these is need for rapid diagnosis to prevent the severity of the disease and mortality.

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