Prader-Willi syndrome (PWS) is a rare neurogenetic disorder, which occurs in 1 per 15,000 live-born children. First described in 1956 by doctors Prader, Labhart and Willi, it is the commonest cause of syndromic obesity in childhood. Diabetes mellitus (DM) is a rare complication of children with PWS. A literature search revealed that most PWS children with DM have required insulin as their treatment while only a couple have responded to oral hypoglycaemic drugs. We report a 11 year old girl with PWS complicated by DM treated with the oral hypoglycaemic drug metformin.

Case report

An eleven year old girl from Weddagala presented to Ratnapura General Hospital with a three week history of polyuria, nocturia and polydipsia. She was born at term, weighing 1800g, to healthy non consanguineous parents following a pregnancy complicated by intrauterine growth retardation. As a newborn she was hypotonic with a feeble cry and feeding difficulties necessitating nasogastric feeding in the neonatal unit for almost a month. Cup and spoon feeding was continued at home for nearly four months by extra-caring parents. Weight gain was poor during the first two years of life but accelerated subsequently as a result of voracious appetite and obsessional overeating.

The developmental milestones were markedly delayed; she began to walk and grasp objects at 3 years and spoke the first clear words at 4 years. Currently she has moderate learning difficulties and special educational needs. In the absence of facilities for special education in her remote hamlet, she does not attend mainstream school but receives elementary education at home. Her appetite remains voracious; she takes five rice meals a day and craves for sugar, sweets and biscuits. Feeling lethargic, she loves to sleep or to remain seated the whole day.

On examination, she was a cheerful, plump girl with a weight of 44 kg (75th-91st centile), height of 123 cm (<0.4th centile) and BMI of 31 kg/m² (>99.6th centile). She has a narrow forehead, small, almond shaped palpebral fissures and small hands and feet. She was hypotonic, pre-pubertal and had a nasal voice. Blood pressure was 100/60 mm Hg (normal for height and age) and examination of other systems revealed no abnormality.

At presentation, 2% of glycosuria without ketonuria and a high blood glucose concentration of 20.9mmol/L were found. The blood urea was 17mg/dl, serum sodium 135mEq/L, serum potassium 4.1mEq/L, Hb 16g/dl, white cell count 12 x 10^9/L with 52% neutrophils, AST 38 U/L, ALT 29 U/L, total cholesterol 166 mg/dl, HDL cholesterol 43mg/dl, LDL cholesterol 101mg/dl, total cholesterol: HDL cholesterol 3.86, triglycerides 109 mg/dl and C peptide 0.89ng/ml. Abdominal ultrasoundography revealed fatty infiltration of the liver.

DM complicating PWS was diagnosed and soluble insulin 0.8 U/kg/day in three divided doses before breakfast, lunch and dinner started. On the 6th day of treatment, when blood glucose concentration decreased to 12mmol/L, insulin was stopped and medication was switched over to oral metformin 250 mg twice daily. Dietary intake of calories was restricted to 2,200 kcal/day and a regular exercise programme was initiated. Dose of metformin was subsequently increased to 500 mg twice daily.

She attained near-normal glycaemia a fortnight after starting metformin with fasting and post-prandial blood glucose readings of 3.3 and 8 mmol/L respectively. Three times daily testing for glycosuria at home revealed negative or 0.5% glucose in more than 90 percent of urine samples. Parents could not afford home blood glucose monitoring. Marked reduction of appetite and lowering of weight by 4 kg over 4 weeks was noticed at follow up clinic visit.
Discussion

PWS is characterized by diminished fetal activity, muscular hypotonia, feeding difficulties and failure to thrive in infancy, hyperphagia and truncal obesity in childhood, short stature, hypogonadotrophic hypogonadism, moderate to severe learning difficulties, behavioural problems, almond shaped eyes and small hands and feet. It is considered as an autosomal dominant disorder and is caused by a deletion of a cluster of genes on the long arm of the paternal chromosome 15 or maternal uniparental disomy 15 because the gene(s) on the maternal chromosome(s) 15 are virtually inactive through imprinting. The initial assumption has been that the DM in this syndrome is simply the result of obesity disputing the hypothesis that the DM in PWS is the result of insulin resistance. Severe insulin resistance in turn leads to pancreatic failure and hence the symptoms complex of type 2 DM. But recent studies have demonstrated that individuals with PWS do not show the predicted insulin resistance that is seen in obese children without the syndrome. In fact, the individuals with PWS showed normal or increased insulin sensitivity disputing the hypothesis that the DM in PWS is simply the result of obesity. Other studies have shown that non-diabetic PWS patients manifest a reduced beta-cell response to glucose stimulation and a significantly increased hepatic insulin extraction compared with obese controls.

Management of DM in PWS include calorie restricted diet, regular exercise and anti-diabetic medication. Since most children with PWS exhibit obsessional overeating consequent to impaired satiety response, dietary restriction of calories has been difficult and unsuccessful. Many PWS children have needed anti-diabetic medication. Insulin has been used in most cases while successful treatment with oral hypoglycaemic drugs is reported only in two children. Only one child treated with metformin is reported in the literature. Metformin, an oral hypoglycaemic drug belonging to the class of biguanides, is the drug of choice in the treatment of type 2 DM in childhood. It acts by increasing tissue sensitivity to insulin, principally in the liver via inhibition of hepatic glycogenolysis. Additional beneficial properties of metformin include a) weight reduction b) favourable effects on the lipid profile c) absence of hypoglycaemia and d) appetite reduction. The weight reduction seen with metformin is in contrast to weight gain caused by insulin and sulphonylureas. Appetite reduction may be of particular significance in diabetes associated with overeating. Our patient achieved near-normal glycaemia and marked weight and appetite reduction with metformin. Lactic acidosis is a rare but important adverse effect of metformin which can occur in children with renal impairment. Hence metformin should be avoided in children with mild renal insufficiency and serum creatinine needs to be measured before and during treatment.

This case illustrates the importance of considering the use of a relatively safe, cheap and easy to administer drug, metformin to treat the uncommon complication of DM, in the rare genetic disorder, PWS.

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References