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Case Report

Managing neonatal diabetes in a resource-challenged setting: a case report on empirical switch to sulfonylurea.

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Abstract

Background: Neonatal diabetes mellitus (NDM) caused by activating mutations in the genes (KCNJ11 or ABCC8), which account for over 50% of cases, frequently responds to sulfonylurea. Sulfonylurea is cost-effective, easy to administer and has better metabolic control. It improves neurocognitive development and has less risk of hypoglycaemia compared to insulin. Identifying patients with mutations in these two genes and hence those who might benefit from sulfonylurea requires genetic testing. In resource-poor settings with zero capacity for genetic testing, an empirical trial of sulfonylurea in all clinically eligible NDM becomes imperative. **Case presentation:** The child is a 7-month-old girl who has been symptomatic for 5-months, referred from a peripheral facility where she was being managed for newly onset type 1 diabetes mellitus with insulin therapy. She was stabilised on insulin; however, she kept having marked fluctuation in blood glucose readings. She was empirically switched to sulfonyl urea at 0.1mg/kg/day in 12-hourly divided doses. She showed marked response to sulfonylurea on the first day of therapy, and insulin was withdrawn, and she maintained perfect glucose readings with no documented hypoglycaemia. **Conclusion**: Neonatal diabetes mellitus remains a challenging case to manage due to its rarity and poor awareness among health care providers, particularly in a poor-resource setting. While insulin therapy remains the cornerstone of therapy at diagnosis, empirical trial of sulfonylurea in all eligible NDM where the capacity for genetic testing is lacking could be rewarding for the patient and managing physician.

Keywords: *ATP-dependent potassium channel, Empirical, sulfonylurea, Neonatal diabetes mellitus.*

Introduction

Neonatal diabetes (NDM) is a form of diabetes mellitus diagnosed in the first six months of life and rarely up to 12 months of age. It is defined as the persistence of insulin-requiring hyperglycaemia in these early months of life.[1] It arises from a single gene mutation affecting the development or function of pancreatic beta cells, leading to insulin deficiency.[2] So far, mutations in over 20 genes linked with the development and function of the pancreas have been described.[3]

The presentation ranges from incidental finding of hyperglycaemia to acute emergency presentation of diabetic ketoacidosis.[4] Common clinical manifestations include small for age at birth, postnatal poor growth, malabsorptive diarrhoea in cases with pancreatic agenesis[2] and neurocognitive disabilities in KCNJ11 mutation.[2,5,6] Phenotypically, NDM is divided into three types, viz: transient, permanent and syndromic neonatal diabetes. Transient neonatal diabetes usually resolves during infancy with normalisation of the blood glucose but may relapse during adolescence or adulthood. In syndromic neonatal diabetes, diabetes is just one of several other components of the disorder, whereas in the permanent type the hyperglycaemia does not remit and diabetes is a stand-alone disorder.[1-3]

The most common cause of permanent neonatal

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diabetes is an activating mutation in the genes (KCNJ11 or ABCC8) encoding the ATP-dependent potassium channel (KATP) of the beta cell. This accounts for greater than 50% of all cases of neonatal diabetes.[2,7] Mutations in these two genes are also the second most common cause of transient neonatal diabetes behind 6q24.[4.] The KATP channel is also expressed in the brain, and its mutation in addition to NDM is associated with a wide range of neurocognitive disabilities, which may include developmental delay and epilepsy (DEND) in the severe form.[8] Other common mutations causing NDM include INS gene, which encodes insulin synthesis, as well as a homozygous mutation in the EIF2AK3 gene, which is the commonest cause of neonatal diabetes among consanguineous couples.[1,9]

The KCNJ11 gene encodes the inner subunit (Kir6.2) of the KATP channel, and ABCC8 encodes the outer subunit (SUR1). This channel closes from a high ATP/ADP ratio, a condition that is usually met following a rise in blood glucose and glucose influx into the beta cell, leading to increased ATP generation via glycolysis. The closure of the channel leads to the depolarisation of the beta cell and ultimately the extrusion of insulin from the cells. Insulin in turn leads to lowering of the blood glucose, hence decreased glucose influx into the beta cells, decreased ATP generation, a fall in ATP/ADP ratio, opening of the channel and a halt in insulin secretion. Heterozygous activating mutations in either of the two genes result in failure of the channel to respond to a rising ATP/ADP ratio from hyperglycaemia, hence remain inappropriately open, leading to the inability of the cell membrane to depolarise and release insulin.[10]

Sulfonylurea binds to the SUR1 subunit, leading to closure of the KATP channel and depolarisation of the beta cell and insulin secretion. It is highly effective in the treatment of neonatal DM caused by mutations in the KCNJ11 and ABCC8 genes. Up to 90–95% of patients with neonatal DM caused by mutations in these two genes can maintain normal blood glucose levels without needing insulin when switched to sulfonylurea.[2,11,12] It has a comparative advantage of improving the neurocognitive disabilities associated with the KCNJ11 mutation, especially when commenced early.[13,14] Several authors have reported improvement in neurocognitive features following switch to sulfonylurea, though such improvement is usually incomplete and tends to plateau after a while.[12,14.] The suboptimal response in neurocognitive features was attributed to inadequate concentration of sulfonylurea in the cerebrospinal fluid and brain to affect the required neuronal electrical activity. [15]

Genetic testing is strongly advocated in every case of NDM, as prognosis and treatment options are highly dependent on the underlying mutated gene. This testing strategy aims to identify those with KCNJ11 or ABCC8 mutations, which are highly sensitive to sulfonylurea therapy. However, in a poor resource setting like ours where genetic services are not available, and the cost of shipping samples to more advanced countries is prohibitive, empirical trial of sulfonylurea therapy becomes imperative after initial stabilisation of the hyperglycaemia with insulin. This is due to the various comparative advantages of sulfonylurea over insulin therapy. We thus report a case of NDM who was empirically switched from insulin to sulfonylurea.

Case Summary

We present a seven-month-old girl child referred from a non-governmental organisation (NGO) facility where she presented with 5 months history of increased breastfeeding, weight loss and 3 weeks history of recurrent fever and passage of loose stool.

Child was observed to have increased demand for breastfeeding; she wakes up 6 to 8 times at night to suck as against her previous feeding habit of 2 to 3 times per night. Mother has been lactating well, and child latches well onto the breast. There is associated history of increased frequency of urination, which mother attributed to the increased breast milk intake. She, however, progressively lost weight despite the increased appetite, compelling the mother to introduce a cereal-based gruel at 4 months of life. The gruel was given 3 to 4 times per day, about 100 mls per feed and was well tolerated, but there was no appreciable improvement in weight. Three weeks before presentation, the child started having fever, which was said to be high, on and off, occasionally relieved by oral paracetamol. At the same time, she started passing loose stool, described as small volume, mucoid, with frequency of 6 to 8 times per day. There was no associated history of vomiting, abdominal distension or refusal to feed. She was taken to a primary health care facility with no improvement; subsequently taken to the NGO clinic where she was admitted for 15 days. At admission, the Random blood glucose was 24mmol/l and glycated Haemoglobin was 7.5%. She was managed as a case of severe acute malnutrition in a newly diagnosed type 1 Diabetes mellitus with insulin, antibiotics, as well as antimalaria (detailed insulin administration could not be retrieved). Ten days into admission, the child

started convulsing, which was generalised, tonic-clonic, lasted 3-5 minutes and was aborted with intravenous diazepam. Following the convulsion, the child lost all acquired milestones and was subsequently referred to our facility for expert care.

She is a product of term pregnancy delivered via spontaneous vaginal delivery. Mother couldn't remember the birth weight, but the child was smaller in comparison to other siblings at birth. Had normal developmental milestones before onset of current illness. She is the third child of the mother in a non-consanguineous marriage. Other siblings are well and alive.

On physical examination, the child was ill-looking, wasted, afebrile (36.7^0C), pale, acyanosed, not jaundiced, with bilateral pitting pedal oedema up to the mid shin. The weight was 4.8kg (-4.15 SDS), length 60 cm (-2.82 SDS) and occipitofrontal circumference 40cm (-2.75 SDS)

Child responded to stimuli, had normal skull and spine, pupils were normal in size and reacted normally to light, there was increased tone in all the limbs. The abdomen was full, moved with respiration, and had hepatomegaly of 4 cm below the costal margin. She was not dyspnoeic or tachypnoeic, with a respiratory rate of 52 cpm, had transmitted sounds all over the chest but no crepitations, and SPO2 was 96%. The heart rate was 146 bpm, regular, good volume; apex beat at 5^{th} left intercostal space mid clavicular line. Heart sounds were 1^{st} and 2^{nd} and were normal.

A working diagnosis of neonatal diabetes with sepsis (Acute bacterial meningitis and acute diarrhoea disease) was made. Admitting random blood glucose was 23.5mmol/l and packed cell volume was 25%.

The serum electrolytes were essentially normal; sodium 138 mmol/l, potassium 3.6mmo/l, chloride 107 mmol/l, and bicarbonate 22 mmol/l. Urea was 3.4 mmol/l, while creatinine was 67 µmol/l. Urinalysis showed glycosuria of +++, Blood +, ketones were negative, and the Specific gravity was 1.025, while PH was 6.0.

She was admitted into the ward. Subcutaneous insulin was commenced at 0.05 iu/kg/dose 8hourly. Intravenous antibiotics and oral zinc were commenced, and blood glucose monitoring was done every three hours before feed (F-100 diluted). The child slowly improved with control of convulsions, normalisation of temperature and her weight appreciated gradually from 4.8 kg at admission to 6.5kg. However, the random blood glucose kept fluctuating, ranging between 12.7 mmol/l and 6.6 mmol/l mostly, with a few hypoglycaemic readings of below 3 mmol/l. Oral Glibenclamide was commenced at 0.1mg/kg/day in 12 hourly divided doses following resolution of acute symptoms. Random blood glucose improved greatly, with all readings within the normal range (7.0 – 3.5mmol/l) over 72 hours of commencement of Glibenclamide. Mother was educated on hypoglycaemic symptoms and home glucose monitoring, and the child was subsequently discharged home for follow-up at the diabetes clinic.

Discussion

Neonatal diabetes mellitus (NDM) remains a challenging case to manage, particularly in poor resource settings like ours. Firstly, NDM is a rare disease with an overall estimated incidence of less than 2 cases per 100,000 infants.[16] This rarity greatly contributes to the lack of awareness of this condition among health care workers. The index case was diagnosed as a case of new-onset type 1 diabetes mellitus from the referring facility. Others include wide variations in clinical presentation and lack of access to genetic studies.

The age at diagnosis of the index case was seven months, which is above the six months of age that accounts for the majority of cases. Although onset after six months of age is not uncommon [(17),] the index patient reported having suggestive symptoms for five months before presentation. Poor health-seeking behaviour and low socioeconomic status could have explained the delay in presentation.

The mother couldn't remember the birth weight of the index patient but reported that she was smaller in size at birth compared to her two other siblings. Low birth weight is a common feature in infants with neonatal diabetes.[18] Since insulin exerts growth-promoting effects during intrauterine development [19], low birth weight in neonatal diabetes mellitus reflects reduced insulin secretion in utero by the foetal pancreas due to β-cell dysfunction.

The major symptoms at diagnosis were increased breastfeeding and weight loss. These are among the classical features of diabetes mellitus. The clinical presentation of NDM varies greatly from persistent hyperglycaemia to diabetic ketoacidosis.[4,20] The current patient has been symptomatic for over 5 months without treatment, and the urinalysis done at admission at our facility was negative for ketones. Although the child had been on insulin from the referring hospital, surviving ketoacidosis for 5 months without insulin is highly unlikely. The other features were fever and diarrhoea; the long-standing malnutrition from the diabetes, as confirmed by the anthropometry and pedal oedema, can explain the

predisposition to infection and diarrhoea from malabsorption.

The blood glucose level at diagnosis of diabetes mellitus from the referring hospital was 24 mmol/l and 23.5 mmol/l at presentation to our facility. These levels of blood glucose are quite high and are well above the diagnostic level for diabetes mellitus.[21] However, the serum bicarbonate was 22 mmol/l and urinalysis was negative for ketones despite the massive glycosuria of 3+. The finding of normal bicarbonate, absence of ketonuria, in addition to the long duration of symptoms without treatment, suggests significant residual insulin secretion. Genetic studies to identify the mutation were desirable but could not be done due to non-availability of such services.

One of the major advantages of genetic testing is the beneficial effect on management if the result returns positive for K_{ATP} Channels mutation. Up to 90 -95 % of neonates with this mutation do well on sulfonylurea alone. [2,11,12] The issue of whether to commence sulfonylurea before receiving the result of genetic testing has not been conclusively settled. While some believe that early commencement enhances intellectual and developmental functions, others are concerned about the risk posed by withdrawal of insulin if the mutation turns out not to be a K_{ATP} Channel mutation.[22] These arguments are valid in a setting where genetic studies are available. In an area that lacks the capacity for genetic testing, empirical trial of sulfonylurea becomes imperative considering the inherent benefit if successful. [23] The index patient was switched to Glibenclamide at the dose of 0.1mg/kg in 12 hourly divided doses according to the recommendation by Rafiq *et al* [7] while still on admission.

The switch from insulin to sulfonylurea can be done either in the in-patient or out-patient setting. However, the in-patient setting may be more appropriate in the case of empirical trial and absence of definitive genetic testing. This will allow for closer monitoring of response and early adjustment of drugs and doses if required. Our patient responded to Glibenclamide on the first day of therapy and insulin was withdrawn. The duration from the start of sulfonylurea therapy to removal of exogenous insulin varies from 1 day to a month. [22]

The index patient showed marked improvement in blood glucose levels following switch to sulfonylurea with less variability in glucose readings following commencement of sulfonylurea. Sulfonylurea therapy has several advantages over insulin in responsive cases. It is associated with better metabolic control[24], and improvement in neurocognitive development and function.[2,13,14] It is also cost-effective and easy to administer, hence the benefit of empirical trial of sulfonylurea under close monitoring in every case of neonatal diabetes in a resource-poor setting where genetic testing is not feasible seems plausible.

Conclusion

Neonatal diabetes mellitus remains a challenging case to manage due to its rarity and poor awareness among health care providers, particularly in a poor resource setting. While insulin therapy remains the cornerstone of therapy at diagnosis, empirical trial of sulfonylurea in the absence of genetic testing could be rewarding for both the patient and managing physician.

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