Neonatal diabetes mellitus due to a rare mutation in KCNJ11 gene

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ABSTRACT

Neonatal diabetes is a heterogeneous group of rare monogenic disorders with an incidence of about 1 in 100,000 live births presenting with in the first 6 months of life with polyuria, dehydration, and ketoacidosis. We, hereby, present a case of neonatal diabetes mellitus due to a very rare mutation (reported 1st time from Indian population) affecting the KCNJ11 gene encoding for KIR6.2 subunit of K_{ATP} channels resulting in inhibition of insulin release and hyperglycemia, leading to permanent neonatal diabetes for which sulfonylurea is the preferred treatment. Instead of insulin injection as endogenous insulin synthesis is not affected unlike other causes of permanent neonatal diabetes mellitus affecting insulin synthesis for which insulin is the only treatment.

Key words: *Diabetes Mellitus, Newborn, Hyperglycemia, Diabetic Ketoacidosis.*

Neonatal diabetes mellitus (NDM) is defined as insulin-requiring persistent hyperglycemia occurring in the first 6 months of life [1]. It is categorized into permanent neonatal diabetes and transient neonatal diabetes [2]. Heterozygous activating mutations, in the KCNJ11 and ABCC8 genes, which encode the Kir6.2 and sulfonylurea receptor 1 (SUR1) subunits of the ATP-sensitive potassium (K_{ATP}) channels that control insulin secretion are the most common and a rarer cause of permanent neonatal diabetes, respectively [3]. It is vital to recognize K_{ATP} channel mutation as most of these patients do not require insulin injections and achieve better glycemic control with sulfonylureas as in the current case. We describe one such case of NDM due to a rare KCNJ11 mutation.

CASE REPORT

This male patient was born of a non-consanguineous marriage without any family history of diabetes or gestational diabetes mellitus in the mother. The patient was born by normal vaginal delivery, weighing 3.5 kg at birth with no history of birth asphyxia. There was a history of two abortions in the mother. The child was being fed on cow milk with 2:1 dilution. At the age of 1.5 months, the patient was presented to us with the complaints of cough and cold for 7 days, fever for 2 days, breathing difficulty for 2 days, and reduced feed acceptance for 1 day. Fever was high grade, not responding to antipyretics, not associated with vomiting, diarrhea, jaundice, with no ear discharge, or crying during micturition. There was no history of cyanosis, feeding diaphoresis, and suck-rest-suck cycle.

When the patient was brought to the hospital, he was febrile (39°C), had tachycardia (210 per min), fast and deep breathing (86/min) associated with chest retraction and grunting sound while breathing, abdominal distension, and opisthotonic posturing. SpO_2 was 60% at admission and increased to 76% with oxygen. Liver and spleen were palpable 2 and 3 cm below costal margin, respectively.

The patient had severe metabolic acidosis with pH of 6.9 with blood sugar >600 mg/dl, hemoglobin of 11.8 g/dl, total leukocyte count 8300/mm^3, and C-reactive protein (CRP) was 23.6 mg/dl. The patient was ventilated for 2 days and managed as diabetic ketoacidosis (DKA) with fluids and IV insulin drip. Anticonvulsant (levetiracetam) was given in view of convulsions and antibiotics (cefotaxime) were given in view of fever and high CRP. Blood culture was sterile. Treatment was started with an intravenous infusion of regular insulin (0.05 U/kg/h); as the condition stabilized, the patient was shifted to subcutaneous insulin after 4 days (Humalog mix sliding scale, 6 hourly monitoring of sugars with dose according to blood sugars).

As NDM is a strong possibility in any child younger than 6 months with persistent hyperglycemia, genetic studies were sent which revealed a heterozygous missense variation in exon 1 of the heterozygous missense variation in exon 1 of the *KCNJ11* gene (chr11:17409037C>T; depth: 10×) that results in the amino acid substitution of histidine for arginine at codon 201 (p.Arg201His; ENST00000339994).

At the age of 3.5 months, the patient developed an episode of fever which precipitated DKA. The patient had to be put on intravenous insulin and was ventilated for 3 days. As the condition stabilized, the patient was shifted to subcutaneous insulin.

After stabilization, the patient was gradually shifted from insulin to oral sulfonylureas (glibenclamide) as this variant of NDM is responsive to sulfonylureas which being an oral drug is a better treatment option. Glibenclamide was started at a dose of 0.1 mg/kg/dose and was gradually increased to 0.8 mg/kg/day, and insulin was gradually reduced accordingly. Blood sugar remained stabilized on this dose. The patient showed normal growth and development on follow-up. Electroencephalography was found to be normal at the age of 5 months.

DISCUSSION

NDM is a rare disease with estimated incidence of 1:300,000–400,000 newborns, although incidence up to 1:89,000 has been reported in some European countries [1,3]. NDM can either be transient NDM (TNDM) or permanent NDM (PNDM). TNDM, more common of the two (50%–60% of all NDM cases) requires initial insulin treatment but resolves spontaneously by a median of 12 weeks of age, only to relapse years later. On the other hand, PNDM requires continuous and lifelong treatment without any period of remission. NDM is a monogenic form of diabetes, with abnormal pancreatic islet development, decreased B-cell mass, or B-cell dysfunction causing insulin deficiency and should be differentiated from autoimmune diabetes which is extremely rare before 6 months, [4].

Approximately, a dozen genes involved in pancreatic development, B-cell apoptosis, or dysfunction are known to cause NDM. The most common cause of PNDM are mutations in the *KCNJ11* gene, which encodes the K_{ATP} channel subunits KIR6.2 (ATP-sensitive inward rectifier potassium channel) and *ABCC8* genes which encode SUR1, [4]. Mutations in genes that encode glucokinase, insulin promoter factor 1, pancreas transcription factor 1α, forkhead box P3 protein, or eukaryotic translation initiation factor 2-alpha kinase 3 are less frequent causes of PNDM [5]. The K_{ATP} channel is a heterotetrameric complex comprising 4 SUR1 and pore-forming KIR6.2 subunits; maintenance of the 1:1 ratio of SUR1:KIR6.2 is essential to both the assembly and function of K_{ATP} [5,6]. In normal pancreatic B-cells, glucose metabolism results in an increased production of intracellular ATP, which binds to the KIR6.2 subunit, causing the potassium channel to close and inhibiting potassium efflux; this subsequently results in cell membrane depolarization, triggering an influx of calcium, and initiating insulin secretion.

Mutations of the *KCNJ11* gene compromise the sensitivity of inhibitory ATP by the KIR6.2 subunit, causing permanent opening of the potassium channel and preventing cell depolarization and insulin secretion [6]. Similarly, activating mutations of the *ABCC8* gene decrease the channel closure and compromise insulin release [5]. Both *KCNJ11* gene and *ABCC8* gene mutations cause insulin deficiency and clinical presentation is same in both. Oral sulfonylurea agents are highly effective in patients with *KCNJ11* gene and *ABCC8* gene mutations, providing better glycemic control than insulin [7,8]. Sulfonylureas bind to the SUR2 subunit of K_{ATP} channel and close the channel in an ATP-independent manner causing membrane depolarization and insulin secretion [9]. Developmental delay, epilepsy, and neonatal diabetes (DEND) is a less common but severe variant of PNDM secondary to K_{ATP} channel mutations that are associated with neurological features. This is believed to be the result of mutated K_{ATP} channels in the brain since both the *KCNJ11* gene and *ABCC8* gene are expressed in neuronal tissue. Milder form with less severe developmental delay and without generalized epilepsy, known as intermediate DEND (iDEND), is more common [7,10].

In any case, presenting with persistent hyperglycemia <6 months, NDM is a strong possibility and genetic screening must be done not only for diagnostic purpose but also it is important for case management (sulfonylureas sensitivity) and genetic counseling. Mutation found in the current case has not been reported from Indian population but similar mutation with different amino acid substitution, affecting the same codon (Arg201Cys), has been reported in the literature [11,12]. The Arg201His variant has not been reported in the genetic database 1000 genomes and ExAC.

The patient with NDM requires regular monitoring for blood sugar levels and long-term complication of diabetes with regular screening for nephropathy and retinopathy [13]. While the course and severity of the disease varies greatly according to the genetic variant, the patient can have a good quality of life and intellectual development with proper care [14].

CONCLUSION

Genetic testing must be done in all cases of persistent hyperglycemia. The majority of patients with K_{ATP} channel mutation responds successfully to oral sulfonylureas, which in comparison to injectable insulin, drastically reduces the complexity of diabetes management and improves the quality of life of the patient.

REFERENCES

1. Grulich-Henn J, Wagner V, Thon A, Schober E, Marg W, Kapellen TM, *et al.* Entities and frequency of neonatal diabetes: Data from the diabetes documentation and quality management system (DPV). Diabet Med 2010;27:709-12.
2. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP, *et al.* Transient neonatal diabetes: Widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000;49:1359-66.
3. Polak M, Cavé H. Neonatal diabetes mellitus: A disease linked to multiple mechanisms. Orphanet J Rare Dis 2007;2:12.
4. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev 2008;29:265-91.
5. Babenko AP, Polak M, Cavé H, Busiah K, Czernichow P, Scharfmann R, *et al.* Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 2006;355:456-66.
6. Hattersley AT, Ashcroft FM. Activating mutations in kir6.2 and neonatal diabetes: New clinical syndromes, new scientific insights, and new therapy. Diabetes 2005;54:2503-13.
7. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008;4:200-13.
8. Shah B, Breidbart E, Pawelczak M, Lam L, Kessler M, Franklin B, *et al.* Improved long-term glucose control in neonatal diabetes mellitus after early sulfonylurea allergy. J Pediatr Endocrinol Metab 2012;25:353-6.
9. Gribble FM, Reimann F. Sulphonylurea action revisited: The post-cloning

era. Diabetologia 2003;46:875-91.
10. Zwaveling-Soonawala N, Hagebeuk EE, Slingerland AS, Ris-Stalpers C, Vulsma T, van Trotsenburg AS, *et al.* Successful transfer to sulfonylurea therapy in an infant with developmental delay, epilepsy and neonatal diabetes (DEND) syndrome and a novel ABCC8 gene mutation. Diabetologia 2011;54:469-71.
11. Liu L, Nagashima K, Yasuda T, Liu Y, Hu HR, He G, *et al.* Mutations in KCNJ11 are associated with the development of autosomal dominant, early-onset Type 2 diabetes. Diabetologia 2013;56:2609-18.
12. Jain V, Satapathy A, Yadav J, Sharma R, Radha V, Mohan V, *et al.* Clinical and molecular characterization of children with neonatal diabetes mellitus at a tertiary care center in northern India. Indian Pediatr 2017;54:467-71.
13. De León DD, Stanley CA. Permanent neonatal diabetes mellitus. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. Gene Reviews. Seattle, WA: University of Washington; 1993.
14. von Mühlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J Med 1995;333:704-8.

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