Clinical Vignette

An Intriguing Case of Neonatal Diabetes Mellitus

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Abstract

Neonatal diabetes mellitus (NDM) is a rare cause of monogenic diabetes diagnosed usually before 6 months of age. We report a case of permanent NDM in a 4-month-old infant girl who presented with diabetic ketoacidosis. She had a past history of refractory epileptic spasms and developmental delay. Genetic analysis showed a heterozygous variant in the *KCNJ11* gene. Around 25% of *KCNJ11* mutations are also associated with neurological features. In this particular child, the clinical features of epileptic spasms, developmental delay and diabetes fit into DEND syndrome which represents one of the most severe forms of permanent NDM.

Keywords: Monogenic diabetes, epilepsy, *KCNJ11*, permanent neonatal diabetes, sulfonylurea

Introduction

Neonatal diabetes mellitus (NDM) presents with hyperglycemia anytime between the neonatal period and infancy, mainly before 6 months of age. It has an incidence of 1 in 90,000 live births with ethnic variability (Iafusco et al., 2012). ATP-sensitive potassium channel mutations (K_{ATP}) constitute the most common cause of permanent neonatal diabetes mellitus (PNDM). K_{ATP} channel is present in the beta cell of pancreas and plays a key role in insulin secretion. This octameric channel is made of two subunits, Kir6.2 and SUR1, coded by the *KCNJ11* and *ABCC8* genes, respectively. Around 25% of *KCNJ11* mutations are associated with neurological features as the K_{ATP} channel is also present in the central nervous system, vascular smooth muscle, and myocardium (Gloyn et al., 2006). We describe a case of NDM with phenotypic features of DEND (Developmental delay, epilepsy, neonatal diabetes) syndrome. It is a rare and severe form of NDM associated with neurodevelopmental delay, motor weakness and epilepsy.

Clinical Report

A 4-month-old female infant, first born to non-consanguineous parents was brought with history of acute onset lethargy and poor feeding. She had a significant perinatal history of being born at term with intrauterine growth retardation (IUGR) by lower segment Caesarean section. Her birth weight was 2.3 kg and she required neonatal intensive care for asymptomatic hypoglycemia and feed intolerance. At 3 months of life, she was diagnosed with epileptic spasms for which she was started on vigabatrin. Magnetic resonance imaging (MRI) of the brain was normal. Electroencephalogram (EEG) showed features of hypsarrhythmia. She did not have social smile and was not recognizing her mother yet. At 4 months of life, in view of poorly controlled spasms, clonazepam and prednisolone were added to the treatment regimen. Within 3 days of starting the new medications the child presented to the emergency room with lethargy and refusal of feeds. There was no family history of neurological disorders or early-onset diabetes mellitus.

On examination, the child was dehydrated, tachycardic and had normal peripheral perfusion. No dysmorphic features were present. Her anthropometric parameters plotted as per the World Health Organization (WHO) growth chart showed weight, length and head circumference at 3rd centile. Systemic examination showed generalized hypotonia. Her capillary blood glucose was 590 mg/dl. Urine ketones were 2+. Venous blood gas showed a pH of 7.12 and bicarbonate of 10.7 mmol/L. This clinical and biochemical picture

was suggestive of moderate diabetic ketoacidosis (DKA). Confirmatory venous random blood glucose was 504 mg/dl and HbA1c was 12.8%. HbA1c, however, cannot be regarded as a reliable indicator of glycemic status below 6 months of age due to the presence of fetal hemoglobin (HbF).

The child was started on intravenous normal saline as per the guidelines of the International Society of Pediatric and Adolescent Diabetes (ISPAD) (Greeley et al., 2022), followed by concurrent insulin infusion at an average rate of 0.04 U/kg/hour. Prednisolone was discontinued. With resolution of DKA, she was started on long-acting insulin glargine, at a dose of 1 unit and pre-prandial rapid acting insulin lispro with 0.5 U adjustment at a dose range of 0.3-0.6 U/kg/day with careful regard to potential hypoglycemia. Pre-feed glucometer blood glucose was checked, and insulin was given for every other feed only if the blood glucose was above 200-250mg/dl in order to prevent hypoglycemia. Anti-epileptic medications were continued as per the pediatric neurologist's advice. However, the child continued to have spasms and on day 4 of hospital stay she was found listless and pale. She required cardiopulmonary resuscitation and while intubating, the findings were suggestive of aspiration. Despite best efforts, the child succumbed and could not be revived.

Genetic testing was performed using a Sanger sequencing-based multigene panel; thirty-six genes associated with monogenic forms of diabetes mellitus were analyzed for pathogenic variations. A novel heterozygous missense variation c.511A>G (p.Thr171Ala) in exon 1 of the *KCNJ11* gene (ENST00000339994) was detected. Segregation analysis showed that both the mother and father of the child did not have this particular variant. This indicated the likely de novo origin of the mutation. The in-silico predictions of the variant are probably damaging by PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) and damaging by SIFT (https://sift.bii.a-star.edu.sg/) and Mutation-Taster2 (https://www.mutationtaster.org/). Based on the American College of Medical Genetics and Genomics and Association for Medical Pathology (ACMG/AMP) guidelines, this variant was classified as 'likely pathogenic' (PS2 + PM1 + PM2 + PP3) (Richards et al. 2015). Thus, the diagnosis for the child was concluded to be DEND syndrome.

Genetic counselling was done for the parents, and they were advised that the risk of recurrence in the next offspring is low though not negligible as germline mosaicism cannot be ruled out.

Discussion

DEND syndrome is a rare, severe form of permanent NDM. The K_{ATP} channel is a key regulator of insulin secretion. Activating mutations in the Kir6.2 subunit cause the K_{ATP} channel to remain open, leading to hyperpolarization of the cell membrane and prevention of Ca2+ influx that is required for exocytosis of insulin into the circulation. In the brain, these channels increase the spontaneous discharge rate of neurons in the ventromedial hypothalamus. IUGR in those affected reflects prenatal insulin deficiency. As described in literature, our case presented after a few months of life with DKA indicating less severe insulin deficiency during the last phase of intrauterine development and at birth. K_{ATP}-NDM is the most common cause of permanent NDM. Ninety per cent of *KCNJ11* mutations cause permanent NDM. The mutation can occur spontaneously (80%) or can be transmitted in an autosomal dominant manner. The mutation identified in our case is a novel de novo variant that has not been reported in literature.

DEND syndrome in India was first reported by Singh et al (2014); the latest follow-up mentioned by them until 2.6 years of age described good glycemic control of diabetes and appreciable improvement in development. Refractory infantile spasms as part of DEND syndrome have been similarly reported by Bahi-Buisson et al. (2007) in a 3-month-old child who also succumbed to aspiration pneumonia at 8 months of life. In a study by Gopi et al. (2021), describing the genotype-phenotype profile of neonatal diabetes mellitus, 20 out of 39 patients had *KCNJ11* mutations, 3 of whom had DEND syndrome – two with the p.Val59Met mutation and one with the p.Val64Met mutation. Severity of developmental delay and epileptic seizures were greater in the patient with p.Val64Met compared to the patients with p.Val59Met; the former also did not respond to sulfonylurea therapy while the latter two patients with p.Val59Met did respond. The two patients with p.Val59Met were also weaned off insulin and continued with sulfonylurea with normal EEG findings off valproic acid. A more severe phenotype is associated with more severe K-ATP dysfunction.

The sulfonylurea class of drugs has been used successfully for treating monogenic NDM affecting the K_{ATP} channel. Often, insulin which is used during initial management after diagnosis of NDM can be completely weaned off in these cases and the child can be transitioned to oral glipalamide. Timely initiation and use of sulfonylurea not only improves glycemic control but also neurodevelopmental outcome. The burden of injections and drug costs resulting from insulin can thus be reduced in cases of NDM that show good response to sulfonylurea.

Conclusion

Permanent NDM caused by *KCNJ11* mutation can rarely present as a severe syndromic form characterized by epilepsy and developmental delay (DEND syndrome) with high risk of early mortality. Neurological features often precede clinical onset of diabetes. Genetic testing forms the most important part of diagnostic evaluation as it helps guide treatment with sulfonylurea drugs.

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Conflict of Interests: None

References

1. Bahi-Buisson N, et al. Infantile spasms as an epileptic feature of DEND syndrome associated with an activating mutation in the potassium adenosine triphosphate (ATP) channel, Kir6.2. J Child Neurol. 2007; 22: 1147-1150.
2. Gloyn AL, et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. Eur J Hum Genet. 2006; 14: 824-830.
3. Gopi S, et al. Genotype-phenotype correlation of K_{ATP} channel gene defects causing permanent neonatal diabetes in Indian patients. Pediatr Diabetes. 2021; 22: 82-92.
4. Greeley SAW, et al. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes. 2022; 23: 1188-1211.
5. Iafusco D, et al. Early Diabetes Study Group of ISPED. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. Acta Diabetol. 2012; 49: 405-408.
6. Richards S, et al. & ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17: 405-424.
7. Singh P, et al. Neonatal Diabetes with Intractable Epilepsy: DEND Syndrome. Indian J Pediatr. 2014; 81:1387–1388.