Transient Neonatal Diabetes Mellitus and Seizure with an Unknown Etiology

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J Pediatr Genet 2023;12:242–245.

Abstract

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes, usually occurring in the first 6 months of life. Here, we present a newborn, which was admitted with epileptic seizure on the postnatal second day of life. Sepsis and meningitis were ruled out. Cranial imaging and electroencephalography revealed normal. She developed transient NDM on the follow-up and was diagnosed to carry an *ABCC8* mutation. Although the neurological features are more common in patients with *KCJN11* mutations, patients with *ABCC8* mutations could also represent with subtle neurodevelopmental changes or even with epileptic seizures. The genetic testing and appropriate therapy is important in this patient group for predicting clinical course and possible additional features.

Keywords
- neonatal diabetes mellitus
- *ABCC8*
- seizure

Introduction

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes, usually occurring in the first 6 months of life, characterized by severe hyperglycemia (>250 mg/dL), which requires insulin treatment. Incidence of NDM is ~1 in 90,000 to 160,000 live births.[1] It is known that diabetes in childhood has been associated with increased mortality and morbidity, but the risk for NDM in infancy remains unclear.

Background

In normal pancreatic β-cells, glucose across the GLUT2 transporter is metabolized by glucokinase enzyme and adenosine triphosphate (ATP) is produced. This results in closure of ATP-sensitive potassium channels (K-ATP channel), depolarization of the cell membrane, and influx of calcium through voltage-gated calcium channels that allow for the exocytosis of insulin granules. *KCJN11* encodes for the inner subunit of the K-ATP channel (Kir6.2), while *ABCC8* encodes for the outer subunit (SUR1), which is the regulatory subunit of the K-ATP channel protein. Mutations in either gene cause K-ATP channels to remain open, even in the presence of hyperglycemia, which prevents insulin release.[1] Activating heterozygous mutations in the genes encoding either subunit of the K-ATP channel (*KCJN11* or *ABCC8*) of the pancreatic β-cells are the most common cause of permanent NDM (PNDM) and the second most common cause of transient NDM (TNDM).[1–3]

NDM is predominantly monogenic in origin and it may be stratified by phenotypic characteristics into three groups as TNDM, PNDM, and syndromic forms.[1] TNDM accounts for 50 to 60% of the NDM cases, requires insulin therapy initially, and then resolves spontaneously within a mean period of 12 weeks. It may relapse to a permanent form of diabetes mellitus later in life.[1,2] Approximately 70% of TDNM cases are caused by anomalies in chromosome 6q24 and 25% by mutations of *KCJN11* and *ABCC8*, which encode either subunit of K-ATP channels of the pancreatic β cells.[3] PNDM is less common than TNDM and it requires lifelong therapy.

received
December 21, 2020
accepted after revision
February 11, 2021
article published online
April 14, 2021

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Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1727175.
ISSN 2146-4596.

Activating heterozygous mutations of *KCJN11* or *ABCC8* are the most common cause of PNDM.[4] Ninety per cent of NDM cases cause TNDM or PNDM, but the remaining 10% are associated with mutations that affect other organ systems besides pancreas. In these cases, clinical features and radiologic evaluation may provide clues to lead the diagnosis.[1]

Clinical Manifestations

Patients with *KCJN11*/*ABCC8* mutations usually represent with NDM before 6 months of age. It was speculated that gestational diabetes mellitus and maternal psychological problems may be a risk factor for NDM.[5,6] The cardinal symptoms of NDM include intrauterine growth retardation (IUGR), failure to thrive, hyperglycemia, dehydration, and rarely diabetic ketoacidosis (DKA). IUGR is seen in >95% of TNDM patients and it is not as prevalent or severe as in cases of PNDM.[1] Hyperglycemia is severe and insulin and C-peptide levels are low or undetectable. Polyuria and polydipsia may present. In neonates, clinical picture may mimic sepsis, which makes diagnosis difficult. DKA is seen more common in PNDM than TNDM and the estimates of DKA frequency at diagnosis vary between 30 and 75%.[7] Macroglossia, umbilical hernia, cardiac anomalies and urinary tract anomalies, hypothyroidism, mild facial anomalies, clinodactyly, polydactyl, nail, and short finger abnormalities are the other clinical features that may be seen in patients with TNDM.[8,9]

Some of the mutations in NDM are related with seizures or epilepsy (►**Table 1**).[8,10] Patients with *KCJN11* mutations, especially permanent form, may suffer from attention deficit hyperactivity disorder, developmental delay, muscle weakness, or treatment-resistant seizures, since K-ATP channels are also expressed in central nervous system. The combination of developmental delay, epilepsy, and NDM is called DEND syndrome. Busiah et al reported that ~25% of NDM patients with mutations encoding K-ATP subunits (*KCJN11* and *ABCC8*) have DEND or intermediate DEND (less severe phenotype in which patients do not have epilepsy).[8]

Diagnosis

NDM should be considered in infants with insulin-dependent hyperglycemia, with blood glucose level persistently >250 mg/dL without an alternative etiology. Initial assessment should include blood gas analysis, serum glucose, C-peptide insulin levels, electrolytes, and urine ketones. Since maternal antibodies may be present up to 6 months of life, testing for insulin autoantibodies is not essential in NDM. Genetic analysis is mandatory in this patient group since it will guide clinical course and appropriate management for the patient.[1]

Table 1 Genetic mutations causing epilepsy in neonatal diabetes mellitus

KCJN11	DEND syndrome
ABCC8	Intermediate DEND syndrome
INS	Epilepsy
IER3IP1	Intractable convulsions
PTF1A	Cerebellar agenesis ± epilepsy
NEUROD1	Cerebellar hypoplasia ± epilepsy

Abbreviation: DEND, developmental delay, epilepsy, and neonatal diabetes.

Management

Most of the patients are managed with insulin during the initial diagnosis and hospital administration. Patients with K-ATP channel mutations have little or no insulin secretion, so they seem to require lifelong insulin treatment. However, sulfonylureas act on K-ATP channels to promote closure and allow insulin to be released from β cells. High-dose oral sulfonylurea may be used in patients with mutations in *KCJN11* and *ABCC8*, which account for ~40% of NDM cases.[1,11] Although there are a few case reports about improvement of neurological functions in patients with *KCJN11* mutations, the impact of sulfonylurea treatment on neurobehavioral and neurologic functions in NDM is not clear yet.[1,8,12–14]

Prognosis

All patients with TNDM need long-term follow-up due to the potential for recurrence of diabetes in adolescents or adulthood. If recurrence occurs, dietary modifications, oral antidiabetic drugs or insulin may be used.[2]

Case Presentation

A female newborn was admitted to the emergency department, with a complaint of convulsion on postnatal second day of life. She was born at 40 weeks of gestation with a birth weight of 2,420 g by normal spontaneous vaginal delivery. Oligohydramnios was detected during the third trimester of the pregnancy.

The parents were first-degree cousins. The mother was diagnosed with gestational diabetes and she had been on diabetic diet without medical treatment. The mother's mother, father, and aunty also had type 2 diabetes mellitus.

Systemic evaluation of the patient was normal. The patient had a second generalized tonic-clonic convulsion, which lasted about a minute in emergency room. Phenobarbital infusion was given and oral phenobarbital was started afterward. Her laboratory evaluation was normal with no signs of infection. Transfontanelle ultrasonography and cranial tomography were also normal. Lumbar puncture was performed to rule out meningitis. Electroencephalography (EEG) revealed normal activity. Although her blood glucose level was within normal range at the administration, it started to increase on postnatal fourth day. Laboratory investigation revealed blood glucose level 280 mg/dL, glucose positive and ketone negative urine analysis, normal blood gas analysis, serum insulin 2.8 μIU/mL (2.6–27 μIU/mL), and C-peptide 1.99 ng/mL (0.9–4 ng/mL). Insulin infusion was started at a dose of 0.01 U/kg/h and increased

up to 1 U/kg/h gradually. On the postnatal sixth day, neutral protamine Hagedorn insulin was started 0.2 U/kg/dose subcutaneously. The dosage was decreased according to blood glucose levels gradually and stopped on postnatal 14th day when preprandial blood glucose levels dropped in between 126 and 185 mg/dL. Abdominal ultrasonography, cardiac echocardiography, auditory tests, and optic nerve evaluation of the patient were normal. Informed consent was received from the family. Sanger sequencing was performed for the diagnosis of NDM. The patient was discharged home with normal blood glucose levels.

Two months after discharge, preprandial blood glucose levels were within the normal range. Genetic test results revealed a heterozygous missense mutation p.Arg1183Trp in the *ABCC8* gene. This was one of the *ABCC8* variants encoding the SUR1 subunit of the K-ATP channel, which have been reported in patients with transient neonatal- and/or adult-onset diabetes. Mother of the patient also had the same mutation. Patient did not have any other epileptic seizures, so phenobarbital treatment was ceased on third month of age. Her anthropometric evaluation was appropriate for her age at the age of 14 months. The neurologic examination and neurodevelopmental tests were also normal.

Discussion

Most of the NDM cases due to *ABCC8* mutations are diagnosed before 6 months of age. TNDM, caused by an *ABCC8* gene mutation, is reported to be more common in males (70%), usually full-term (76%) and low-birth-weight (56%) infants, presenting in between 3 and 60 days.[1,15] Docherty et al reported that macroglossia (50%), umbilical hernia (25%), cardiac and renal anomalies (9%), hand anomalies (8%), and hypothyroidism (4%) may be seen in patients with TNDM.[9] Our patient was a full-term female newborn, which had a low birth weight and no other clinical features, present on postnatal second day. She recovered within 12 weeks as specified in the literature.

In the past two decades, several gene defects underlying different forms of epilepsy, most of which code for ion channels, were identified. K-ATP (Kir1–7) channels are one of these ion channels, which are present in neuronal cells and couple cell metabolism to cell excitability. Mutations in Kir6.2 (*KCJN11*) or SUR1 (*ABCC8*) subunits cause a decrease in the ability of ATP to block the K-ATP channel. As a result, channels are opened more fully in the physiological relevant concentrations of ATP and increase ATP current.[16] Although the pathophysiologic mechanism leading to epilepsy is still uncertain, one of the hypotheses is that elevated levels of extracellular glucose and intracellular ATP attenuate K-ATP channels, producing a more excitable state.[17] DEND syndrome is usually seen in patients with PNDM due to a *KCJN11* mutation. The association between PNDM with *ABCC8* mutations or transient forms of either gene is uncertain.[1,8]

Ovsyannikova et al reported a patient, who had a history of grand mal epilepsy between the age of 3 and 10 years, atrophic loci in periventricular white matter on magnetic resonance imaging, presented with diabetes mellitus at the age of 27 years, and diagnosed *ABCC8* mutation.[18] Although most of the patients with *ABCC8* mutations do not have neurological features, muscle weakness, developmental delay, dystonia, motor visual, and spatial dyspraxia are reported in some of the patients.[3,19]

Flanagan et al reported a case, which had the same mutation as our patient, presented with tonic posturing with right facial involvement and two generalized seizures prior to insulin therapy and did not have further seizure episodes afterward. They related this condition to DKA and hyperglycemic state of the patient. There was no additional information about neurodevelopmental outcome of the patient.[3] Batra et al reported another patient with the same mutation and TNDM, who presented on postnatal second month with focal seizure, diagnosed DKA, and had a general seizure 2 days after admission while he was on insulin therapy. This patient developed mild mental retardation and severe developmental delay on the follow-up. The neurologic clinical picture of the patient was related to hyperglycemia and hyperosmolality.[15] Different from these cases, our patient did not have high glucose levels before or during the seizure, which might explain the seizures with state of hyperglycemia or hyperosmolality. The EEG, cranial computerized tomography, and metabolic evaluation were also normal. A study of Hernández-Sánchez et al showed that transgenic mice, overexpressing the SUR1 gene, show significant increase in the threshold for kainite-induced seizures.[20] Although we do not have a clear explanation for the etiology of the seizure, we hypothesize that due to the missense mutation of the SUR1 gene and a decreased expression of normal SUR1 gene, threshold for the seizure might decrease, neuronal cells might get hyperexcitable independent of serum glucose levels and caused seizure in our patient.

Busiah et al concluded that most patients with K-ATP channel mutations have neurological and neurodevelopmental impairments, so that the patients with NDM or adult diabetic patients with history of hyperglycemia before 1 year of age should undergo routine genetic and neurodevelopmental testing.[8] Our patient had normal neurodevelopmental progress. Her Denver Developmental Screening Test was appropriate for her age at the age of 14 months. She did not have any other seizures and her HbA1c level was within normal range.

Conclusion

Early detection of NDM, genetic testing, and appropriate therapy are important to improve patient outcomes. Although neurological features are more common in association with *KCJN11* mutations, we should be aware that patients with *ABCC8* mutations could also represent with subtle neurodevelopmental changes or even with epileptic seizures.

Conflict of Interest
None declared.

References

1 Lemelman MB, Letourneau L, Greeley SAW. Neonatal diabetes mellitus: an update on diagnosis and management. Clin Perinatol 2018;45(01):41–59

2 Temple IK, Shield JP. Transient neonatal diabetes, a disorder of imprinting. J Med Genet 2002;39(12):872–875

3 Flanagan SE, Patch AM, Mackay DJG, et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes 2007;56 (07):1930–1937

4 De Franco E, Flanagan SE, Houghton JA, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet 2015;386 (9997):957–963

5 Lee KW, Ching SM, Hoo FK, et al. Neonatal outcomes and its association among gestational diabetes mellitus with and without depression, anxiety and stress symptoms in Malaysia: a cross-sectional study. Midwifery 2020;81:102586

6 Lee KW, Ching SM, Devaraj NK, et al. Diabetes in pregnancy and risk of antepartum depression: a systematic review and meta-analysis of cohort studies. Int J Environ Res Public Health 2020;17 (11):3767

7 Letourneau L, Carmody D, Wroblewski K, et al. Diabetes presentation and management in infancy: high risk of diabetic ketoacidosis. Diabetes Care 2017;40:e147–e148

8 Busiah K, Drunat S, Vaivre-Douret L, et al; French NDM study group. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study [corrected]. Lancet Diabetes Endocrinol 2013;1(03):199–207

9 Docherty LE, Kabwama S, Lehmann A, et al. Clinical presentation of 6q24 transient neonatal diabetes mellitus (6q24 TNDM) and genotype-phenotype correlation in an international cohort of patients. Diabetologia 2013;56(04):758–762

10 Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. Horm Res Paediatr 2013;80(03): 137–146

11 Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic β-cell diabetes. Nat Clin Pract Endocrinol Metab 2008;4(04):200–213

12 Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of *KCNJ11* mutation testing in neonatal DM. Pediatr Diabetes 2010;11(03):203–207

13 Mlynarski W, Tarasov AI, Gach A, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in *KCNJ11*. Nat Clin Pract Neurol 2007;3(11):640–645

14 Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the *KCNJ11* gene. Diabetologia 2006;49(11):2559–2563

15 Batra CM, Gupta N, Atwal G, Gupta V. Transient neonatal diabetes due to activating mutation in the *ABCC8* gene encoding SUR1. Indian J Pediatr 2009;76(11):1169–1172

16 Villa C, Combi R. Potassium channels and human epileptic phenotypes: an updated overview. Front Cell Neurosci 2016;10:81

17 Huang CW, Huang CC, Cheng JT, Tsai JJ, Wu SN. Glucose and hippocampal neuronal excitability: role of ATP-sensitive potassium channels. J Neurosci Res 2007;85(07):1468–1477

18 Ovsyannikova AK, Rymar OD, Shakhtshneider EV, et al. ABCC8-related maturity-onset diabetes of the young (MODY12): clinical features and treatment perspective. Diabetes Ther 2016;7(03):591–600

19 Patch AM, Flanagan SE, Boustred C, Hattersley AT, Ellard S. Mutations in the *ABCC8* gene encoding the SUR1 subunit of the KATP channel cause transient neonatal diabetes, permanent neonatal diabetes or permanent diabetes diagnosed outside the neonatal period. Diabetes Obes Metab 2007;9(Suppl 2):28–39

20 Hernández-Sánchez C, Basile AS, Fedorova I, et al. Mice transgenically overexpressing sulfonylurea receptor 1 in forebrain resist seizure induction and excitotoxic neuron death. Proc Natl Acad Sci U S A 2001;98(06):3549–3554