Case Report

Sequence Analysis of Common Gene Mutation for Neonatal Diabetes: Three Case Series Report of Neonates with Severe Neonatal Hyperglycaemia

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Abstract

Neonatal diabetes mellitus (NDM) is a rare disorder characterized by persistent hyperglycaemia within the first six months of life, resulting from inadequate insulin production, hence the need for exogenous insulin therapy. This persistent hyperglycaemia can be life-threatening and often associated with adverse consequences if undiagnosed. Hence, the need for high index of suspicion, prompt investigation and early diagnosis, in an attempt to provide appropriate and cost-effective therapy. We report three cases of infants that presented with persistent hyperglycaemia and were managed for neonatal diabetes. The infants had their blood glucose done at presentation using a glucometer (Accu-chek Active® Roche Diagnostics GmbH, Germany). Blood samples for the genetic test were aseptically taken from each infant and inoculated into EDTA bottles, stored in a refrigerator, and later transported within 24hrs through courier service in an ice pack flask to the molecular genetics' laboratory at the University of Exeter, United Kingdom, for genetic studies for *KCNJ11*, *ABCC8*, and *INS* genes. The three babies had clinical features of neonatal diabetes and received insulin therapy as part of management; however, the genetic analysis did not identify any mutation. Newborn babies can present with hyperglycaemia from varied causes, of which NDM, though rare, is one of them. We recommend early investigation of the cause of hyperglycaemia, and in the exclusion of common causes, extensive genetic studies including other implicated genes such as *FOXP3*, *GLUT2*, and *IPF1*, should be considered.

Keywords: *ABCC8* gene, gene mutation, *KCNJ11* gene, neonatal diabetes mellitus, neonatal hyperglycaemia

Introduction

Neonatal diabetes mellitus (NDM) is a rare disorder (1:300,000–400,000 newborns) characterized by persistent hyperglycaemia within the first six months of life.[1,2] It results from inadequate insulin production with consequent hyperglycaemia, hence the need for exogenous insulin therapy.[2,3] It presents as intrauterine growth restriction (IUGR) and failure to thrive (FTT) in the newborn.[1-3] More than 20 genetic causes have been identified as possible aetiologies, with mutations in pancreatic beta-cell K-ATP channel genes (*KCNJ11 and ABCC8*) being the most common.[4,5] A diagnosis of NDM should be entertained in a newborn with hyperglycaemia of ≥250 mg/dl in the absence of any other aetiology, persisting for more than one week.[4] The cutoff value of hyperglycaemia in a newborn at which treatment should be commenced is ill defined.[4] Early diagnosis of NDM is of utmost importance as it guides the management and the need for alternative therapies such as sulfonylureas.[6]

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We report three cases of NDM that presented with hyperglycaemia after an uneventful term pregnancy, labour, and immediate postnatal periods. Baby 1 and baby 2 presented at the newborn special care unit in May and September

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2020, respectively, while baby 3 presented at the children's emergency room in July 2021 at the Alex Ekwueme Federal University Teaching Hospital, Abakaliki, in Southeast Nigeria. Blood samples were aseptically collected for microscopy culture and sensitivity before the commencement of antibiotics in all three cases to rule in/out sepsis; however, the results came out negative.

Baby 1 was a two-week-old male first seen on the 10th day of life with complaints of fever, irritability, and restlessness of one-day duration. On examination, there were signs of dehydration, and the anthropometric index that was severely affected was the weight (2.35 kg), which was below the 3rd percentile for age. Birth weight was not known, the body length on presentation was 50 cm, and occipitofrontal circumference (OFC) was 35 cm. The random blood sugar on presentation was >600 mg/dl. Other laboratory results are shown in Table 1. The child was admitted, and subcutaneous insulin, parenteral fluid, and antibiotics were commenced. The duration of admission was 11 days and was followed up weekly until resolution of hyperglycaemia at three months of age.

Baby 2 was a six-week-old male who presented with progressive weight loss, diarrhea, and poor suck of two weeks duration. On examination, there were signs of dehydration. The birth weight was 3.8 kg, while the weight on admission was 2.25 kg, which was below the 3rd percentile for age. The body length on presentation was 53 cm and OFC was 35.5 cm. The random blood sugar on presentation was 332 mg/dl. Other laboratory results are shown in Table 1. The child was admitted, and subcutaneous insulin, parenteral fluid, and antibiotics were commenced. The duration of admission was eight days, and the child was lost to follow-up.

Baby 3 presented at 11 weeks of age with FTT and hyperglycaemia that was discovered at a routine immunization clinic. There was a history of episodes of convulsion and apneic spells. On examination, there were signs of dehydration. The birth weight was not known, but the weight on admission was 4.3 kg, which was below the 3rd percentile for age. The body length on presentation was 57 cm and OFC was 37 cm. The random blood sugar on presentation was 241 mg/dl. Other laboratory results are shown in Table 1. The child was also admitted and subcutaneous insulin, parenteral fluid, and antibiotics were commenced. He had a few episodes of convulsion and poorly controlled blood sugar and died on the seventh day of hospitalization. All three infants received a preprandial subcutaneous insulin 0.05 IU/kg/dose with every other feed (3–4 × daily). Venous blood samples for the genetic test were aseptically taken from each of the infants and inoculated into EDTA bottles, stored in a refrigerator, and later transported within 24hrs through courier service in an ice pack flask to the molecular genetics laboratory at the University of Exeter, United Kingdom, for genetics' studies for *KCNJ11*, *ABCC8, and INS* genes. Results for the three specific genes were negative.

Table 1: Laboratory parameters of three infants with neonatal hyperglycaemia

Laboratory parameter	Baby 1	Baby 2	Baby 3
Average RBG on presentation (mg/dl)	High (>600)	332	241
Urinalysis	Sugar+, ketone+	Sugar+++, ketone−ve	Sugar+, ketone−ve
Blood culture	Negative	Negative	Negative
KCNJ11/ABCC8/INS genes	Negative	Negative	Negative
RBG			

RBG: Random blood glucose, INS: Insulin

Discussion

NDM, also referred to as early-onset or congenital diabetes mellitus, is a rare medical condition.[1] A case was previously reported in Southwest Nigeria[7] and few in other African countries.[8,9] It is most often from a genetic origin, and recent genetic advances show that it results from mutations in a single gene, hence a monogenic defect.[1,4] Activation mutation of *KCNJ11* and *ABCC8*, which encodes the K_{ATP} subunits KIR6.2 (ATP-sensitive K + channel, a lipid-gated, inward-rectifier potassium ion channel) and SUR (sulfonylurea receptor) is known to be responsible for most cases of neonatal diabetes.[1,4] Other gene mutations involved are *INS* gene, chromosome 6q24, FOXP3, GCK, IPF1, PTFIA, EIF2AK3, GLUT2, HNFIB, and GLIS3.[3-5] Clinical features include IUGR, FTT, ketoacidosis, vomiting, and dehydration.[2,3] The babies showed features suggestive of FTT. In the newborn, other causes of hyperglycaemia such as sepsis, stress, steroid medications, and glucose infusion make the diagnosis of NDM difficult. However, hyperglycaemia usually resolves within 10 days of life.[10] In the index cases, hyperglycaemia was noted from at least the second week of life and persisted beyond one month of age.

According to the phenotypic characteristic, NDM has been categorized as transient (TNDM), permanent (PNDM), and sometimes, part of a syndrome.[11,12] Majority of NDM are transient (50%–60%).[11,12] Unlike the PNDM, the TNDM resolves in the postnatal period, usually within the first year of life, though cases of persistence or recurrence of diabetes mellitus (nonautoimmune Type 1) in later life have been noted.[11,12] Baby 1 appears to have features suggestive of TNDM, as the hyperglycaemia resolved at three months of age. However, such may not be said about the others. In a newborn with NDM, no confirmed clinical markers predict if it is TNDM or PNDM. However, molecular studies have ascribed some particular gene mutations as a common aetiology of TNDM and PNDM.[2] Some postulations and conclusions have been reached in an attempt to differentiate the two: (1) higher prevalence of IUGR, younger age of presentation, lower exogenous insulin requirement, lower likelihood of ketoacidosis, and the higher likelihood of persistent/recurrent diabetes mellitus in TNDM, though with significant overlap

with PNDM and (2) chromosome 6 mutation is usually associated with TNDM, while mutations in pancreatic beta-cell K-ATP channel genes (*KCNJ11* and *ABCC8*) account for 50% of PNDM.[2] It has been recommended that genetic testing should be carried out if hyperglycaemia persists for more than two weeks.[4,13] In TNDM, even with the resolution of hyperglycaemia, genetic testing is still recommended due to the risk of recurrence.[4] The absence of the three genes studied in the index cases does not rule out NDM, as more than 20 genetic causes have been identified as possible aetiologies, with mutations in *KCNJ11* and *ABCC8* being the most common.[4,5] Other genes (especially for PNDM) include insulin gene (*INS*), *FOXP3*, *GLUT2*, and *IPF1* genes.[3-5]

An early institution of insulin has been shown to be useful as it encourages adequate weight gain, even in those with IUGR.[2] Subcutaneous insulin has been shown to be satisfactory and helps avoid the complications associated with the central venous catheter used for infusion therapy. A preprandial dose of 0.1–0.15 units/kg/dose with every other feed (3–4 times/day) of short-acting insulin has been recommended.[4]

The prognosis depends on the metabolic control and severity of the disease, age of diagnosis, and treatment.[2] This was evident in the outcomes of the 1st and 3rd index cases who had early and late hospital presentations, respectively. We recommend early commencement of insulin and further evaluation of other genes implicated in NDM.

Limitation of the study

Other genes implicated as a cause of neonatal hyperglycaemia such as FOXP3, GLUT2, and IPF1 were not evaluated.

Conclusion

Although the three cases had clinical features of neonatal diabetes, genetic analysis for *KCNJ11*, *ABCC8*, and *INS* genes did not identify any mutation. It is essential to identify babies with neonatal diabetes and exclude the possibility of gene mutations early by carrying out an extensive genetic study including other implicated genes such as *FOXP3*, *GLUT2*, and *IPF1*.

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Conflicts of interest

There are no conflicts of interest.

References

1. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev 2008;29:265-91.
2. Polak M, Cavé H. Neonatal diabetes mellitus: A disease linked to multiple mechanisms. Orphanet J Rare Dis 2007;2:12.
3. Fösel S. Transient and permanent neonatal diabetes. Eur J Pediatr 1995;154:944-8.
4. Lemelman MB, Letourneau L, Greeley SA. Neonatal diabetes mellitus: An update on diagnosis and management. Clin Perinatol 2018;45:41-59.
5. Shah RP, Spruyt K, Kragie BC, Greeley SA, Msall ME. Visuomotor performance in KCNJ11-related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. Diabetes Care 2012;35:2086-8.
6. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue K; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2006-2007. The diagnosis and management of monogenic diabetes in children. Pediatr Diabetes 2006;7:352-60.
7. Akinola IJ, Odusote OA, Oduwole AO. Neonatal diabetic ketoacidosis in a Nigerian infant: A case report. Nig Q J Hosp Med 2015;25:139-41.
8. Nyangabyaki-Twesigye C, Muhame MR, Bahendeka S. Permanent neonatal diabetes mellitus-A case report of a rare cause of diabetes mellitus in East Africa. Afr Health Sci 2015;15:1339-41.
9. Abacı A, Razi CH, Ozdemir O, Hızlı S, Kıslal F, Argas PI, *et al.* Neonatal diabetes mellitus accompanied by diabetic ketoacidosis and mimicking neonatal sepsis: A case report. J Clin Res Pediatr Endocrinol 2010;2:131-3.
10. Rozance PJ, Hay WW. Neonatal hyperglycaemia. NeoReviews 2010; 11:e632-9.
11. von Mühlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J Med 1995;333:704-8.
12. Shield JP, Gardner RJ, Wadsworth EJ, Whiteford ML, James RS, Robinson DO, *et al.* Aetiopathology and genetic basis of neonatal diabetes. Arch Dis Child Fetal Neonatal Ed 1997;76:F39-42.
13. Ogilvy-Stuart AL, Beardsall K. Management of hyperglycaemia in the preterm infant. Arch Dis Child Fetal Neonatal Ed 2010;95:F126-31.