Editorial

A Rare Case Report of Familial Neonatal Diabetes Mellitus

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Abstract

Neonatal diabetes mellitus (NDM) is a rare form of diabetes characterized by hyperglycemia occurring in the first few months of life with incidence 1 in 300,000 to 400,000 newborns. It is classified as transient and permanent type. Genetic etiology of this disease has been identified. Most of the TNDM cases are caused by the overexpression of chromosome 6q24, and the majority of PNDM cases are due to KATP channel mutations caused by heterozygous activating mutations in *KCNJ11* and *ABCC8.* INS gene mutations can be inherited in both autosomal dominant and recessive pattern. Hereby we present a familial case of neonatal diabetes due to INS gene mutation.

Key words: Hyperglycemia, Newborn, Diabetes mellitus, Insulin

Introduction

The term "Neonatal Diabetes" was first coined by Gentz & Cornblath [1]. Kitselle in 1852 first described this disorder clinically, which was present in his son [2,3,]. Neonatal diabetes presenting as uncontrolled hyperglycemia during the first 6 months of life is a rare monogenic disorder with the incidence of 1 in 300,000 - 4,00,000 newborns [4]. It affects all races and ethnic groups and presents with IUGR, failure to thrive, decreased SC fat, and low or undetectable C-peptide levels [5]. Hutchinson et al. first distinguished the permanent (PNDM) vs. the frequently relapsing transient (TNDM) forms of neonatal diabetes [6]. Transient form occurs within first few weeks of an infant's life & accounts for 50% to 60% of all NDM cases [7]. Permanent type is less common and requires lifelong treatment. Hyperglycemia in TNDM resolve spontaneously by 12 weeks of age, only to relapse later during adolescent period [8]. The genetic mutations causing neonatal diabetes have been identified now and familial cases occurs due to genetic etiology.

Case Report

A full term, IUGR, 1.63 kgs, male baby born by LSCS to a G2P2D1 mother was brought with h/o high blood sugar levels at birth. No h/o gestational diabetes in mother. Baby cried immediately and had good Apgar score. H/o previous sibling death on day 21 of life due to Persistent hyperglycemia & sepsis present. At admission: HR- 164/min, RR- 68/min, SPO2 – 98%, GRBS- High (480mg/dl), temperature – normal. Systemic examination -normal. Weight, length and OFC were below 3rd percentile. Baby was treated with IVF, Oxygen, antibiotics & supportive measures. Investigations – Hb: 16 mg/dL, WBC: 18,200 cells/cu mm, Platelet count: 3, 30,000/cu mm, CRP negative. Blood C/S sent was negative after 48 hrs. Small amount of feeds were started and upgraded as baby tolerated. On day 3, baby developed abdominal distention and feed intolerance. Repeat septic screen was strongly positive. Antibiotics were hiked up accordingly. Baby was kept NPO for 72 hrs and then slowly feeds were resumed & upgraded to full feeds by day 12 of life. In v/o serial high GRBS (all readings above 400mg/dl), Pediatric Endocrinologist Opinion was taken & insulin infusion was started.

Investigations showed: Urine ketones negative. C-Peptide levels were low (0.2 ng/ml). HbA1C at 7 days of life was 4.9%. Lipid panel, liver enzymes, sr.electrolytes and ionic calcium were in normal limits.

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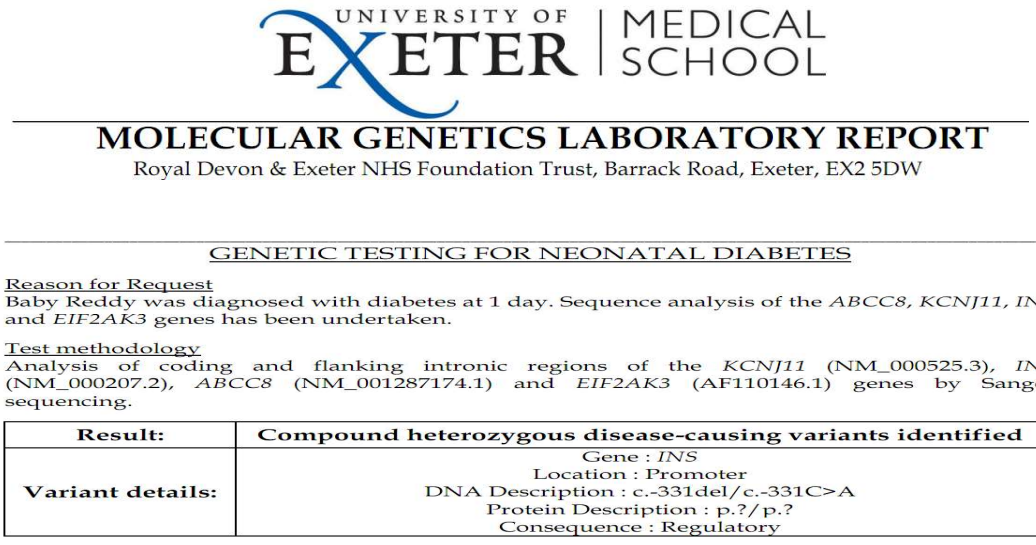
After initial continuous insulin infusion baby was treated with combination insulin therapy with inj. Lispro and inj. Lantus. GRBS levels were periodically monitored. In v/o frequently fluctuating GRBS values, injinsugen-N was started. Baby improved with treatment & GRBS maintained within normal range with initial fluctuations. Insulin dosage was adjusted according to endocrinologist opinion. The genetic testing for the baby & parents were done at Molecular Genetic Laboratory Exeter, UK, which showed that baby was compound heterozygous for two INS promoter variants (c.-331 del/c.-331c>A) which were predicted to be pathogenic and hence genetic diagnosis of recessively inherited neonatal diabetes due to disease causing variants in INS gene was confirmed. Genetic analysis for both the parents confirmed that parents were heterozygous for one of the 2 variants and were carriers of neonatal diabetes. Being autosomal recessive inheritance the risk of couple's next pregnancy to be affected is 1 in 4. Parents were educated about the disease & trained for insulin administration. High calorie diet & regular follow up was advised for adequate growth & development.

Discussion

NDM is a monogenic form of diabetes (usually caused by a single gene mutation) resulting from abnormal pancreatic islet development, decreased B-cell mass, or B-cell dysfunction [9]. Being monogenic, its incidence is higher in the geographical regions with high rates of consanguinity, as seen in our subject family [10]. Parents of our baby had second degree consanguinity. H/o earlier sibling death on day 21 of life with severe persistent hyperglycemia (Suspected Neonatal diabetes) and sepsis was strong pointer towards the familial onset of neonatal diabetes**.** The genetic etiology in neonatal diabetes varies as the mode of inheritance varies widely for the genes involved. 70% of TNDM cases occurs due to defects causing over expression of paternally expressed genes in the imprinted region of chromosome 6q24 [11]. Paternal UPD6 (partial or complete) accounts for the majority of sporadic cases [12]. Permanent NDM is a result of K_{ATP} channel mutations caused by heterozygous activating mutations in *KCNJ11* and *ABCC8* [13]. Mutations in the insulin gene itself cause 12% of PNDM. In our case, samples were sent to EXETER molecular genetics laboratory UK which showed that baby had mutations in INS gene. Baby was compound heterozygous for two INS promoter variants (c.-331 del/c.-331c>A) which were pathogenic. Mutations in INS gene can be both dominant and recessive in inheritance. The phenotype in recessive inheritance is more severe than with dominant mutations, leading to earlier presentation and lower birth weight [14]. Our baby had recessively inherited mutations, hence presented very early in life & had low birth weight. Both parents were carrier for neonatal diabetes.



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MOLECULAR GENETICS LABORATORY REPORT

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GENETIC TESTING FOR NEONATAL DIABETES

Reason for Request

Baby Reddy was diagnosed with diabetes at 1 day. Sequence analysis of the *ABCC8, KCNJ11, INS* and *EIF2AK3* genes has been undertaken.

Test methodology

Analysis of coding and flanking intronic regions of the *KCNJ11* (NM_000525.3), *INS* (NM_000207.2), *ABCC8* (NM_001287174.1) and *EIF2AK3* (AF110146.1) genes by Sanger sequencing.

Result:	Compound heterozygous disease-causing variants identified
Variant details:	Gene : *INS* Location : Promoter DNA Description : c.-331del/c.-331C>A Protein Description : p.?/p.? Consequence : Regulatory

- IUGR is seen in >95% of TNDM patients, and the birth weight typically ranges from 1.5−2.5 kg. [15]. Our baby was term IUGR weighing 1.63kgs which was similar to findings of 2002 French Cohort study which showed that 74% cases of TNDM and 36% PNDM cases were IUGR.
- Both sex are affected with slight male preponderance. In our case both the index case and the earlier sibling who died of severe hyperglycemia were males.
- The mainstay of the management is insulin, regardless of the etiology [9]. Babies with KATP channel mutations responds well to oral sulfonylurea [16,17]. In our case, baby started maintaining GRBS in normal range after insulin therapy. Parents were taught to monitor GRBS and administer insulin. High calorie diet & regular follow up was advised to monitor growth & development.

Conclusion

NDM is a rare disease that presents as either the TNDM or PNDM form. Insulin therapy is crucial to control hyperglycemia and obtain satisfactory weight gain and growth. Patients with KATP channel mutation respond successfully to oral sulfonylurea therapy. High index of suspicion, early diagnosis & prompt treatment is the key to decreases the complexity of diabetes management and to provide a better quality of life.

Abbreviations

1. NDM- neonatal diabetes mellitus.
2. TNDM- transient neonatal diabetes mellitus.
3. PNDM- permanent neonatal diabetes mellitus.
4. IUGR - intrauterine growth retardation.
5. GRBS- general random blood sugar.

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References

1.Gentz JC, Cornblath M 1969 Transient diabetes of the newborn. Adv Pediatr 16:345–363.

2. Attia N, Zahrani A, Saif R, Kattan HA, Sakati N, Al AshwalA,TamborlaneWV 1998 Different faces of non-autoimmune diabetes of infancy.Acta Paediatr87:95–97.

3. Shield JP 2000 Neonatal diabetes: new insights into aetiology and implications.Horm Res53(Suppl1):7–112.

4.Grulich-Henn J, Wagner V, Thon A, et al. Entities and frequency of neonatal diabetes: data from the diabetes documentation and quality management system (DPV). Diabet Med. 2010;27(6):709–712.

5. Fosel S 1995 Transient and permanent neonatal diabetes. Eur J Pediatr 154:944–948

6. Hutchinson JH, Keay AJ, Kerr MM 1962 Congenital temporary diabetes mellitus. BMJ 2:436–440

7.Anglina Kataria, Resmy Palliyil Gopi, Pradeep Mally, Bina Shah. Neonatal diabetes mellitus: current perspective. Research and Reports in Neonatology 2014: 4:55-63.

8. Temple IK, Gardner RJ, Mackay DJ, *et al.* Transient neonatal diabetes mellitus: widening our understanding of the aetiopathogenesis of diabetes. Diabetes 2000; 49: 1359–1366

9.Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev. 2008;29(3):265–291.

10.Michael Yafi. A Case of Neonatal Diabetes Presentation, Diagnosis and Management. Austin J Pediatr. 2014;1(1): 1004.

11.Abdollahi A. LOT1 (ZAC1/PLAGL1) and its family members: mechanisms and functions. J Cell Physiol. 2007; 210(1):16–25.

12. Mackay DJ, Temple IK. Transient neonatal diabetes mellitus type 1. Am J Med Genet C Semin Med Genet. 2010;154C(3):335–342.

13.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(4):200–213.

14.Garin I, Edghill EL, Akerman I, *et al.* Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. PNAS 2010; 107: 3105–3110.

15. Mackay DJ, Temple IK. Transient neonatal diabetes mellitus type 1. Am J Med Genet C Semin Med Genet. 2010;154C(3):335–342.

16.Pearson ER, Flechtner I, Njølstad PR, et al; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006; 355 (5):467–477.

17. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT; Neonatal Diabetes International Collaborative Group. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care. 2008;31(2):204–209.

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