European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 02, 2023

Original Research Article

Heterozygous neonatal DM: Case report

[1]Dr. S Ranjith Pratap, [2]Dr. E Suresh

[1]Assistant Professor, Institute of Diabetology, Stanley Medical College, Chennai, Tamil Nadu, India

[2]Director and Professor, Institute of Diabetology, Stanley Medical College, Chennai, Tamil Nadu, India

Corresponding Author:
Dr. S Ranjith Pratap

Abstract

Abstract

Chronic increase and high level of glucose results in a metabolic disorder termed as Diabetes Mellitus. Diabetes occurs as a result of some genetic factors, namely the mutations of single gene. Permanent neonatal diabetes is very rare form of disorder, termed as monogenic diabetes. This type of rare diabetes presentation is seen in the child of age less than 6 months.

Presenting the single case of neonatal diabetes reported from Chennai. A 2 month old female child is actually diagnosed with permanent neonatal diabetes-4 because of the heterozygous mutation of INS gene present in chromosome 11p15.

Though the occurrence of permanent neonatal diabetes is very rare, this diagnosis has to be made when the infants are presenting with features of persistent hyperglycaemia and also in need of the insulin therapy. Children with the INS mutation will exhibit overall good prognosis when they are adequately managed with insulin therapy.

Key words: INS gene, diabetic ketoacidosis, neonatal diabetes

Introduction

Chronic rise in the glucose levels results in a metabolic disorder termed as Diabetes Mellitus. The disorder is seen in any age group individual right from birth. Among various factors responsible for this disorder, genetic factors are considered to play a vital role. Mutation in a single gene will also result in the occurrence of this disorder and found to have a pathogenic role [1-5].

The disorder presenting in the infancy is further classified into permanent and transient neonatal diabetes. They both will have the hyperglycemia in the period of infancy. In transient type, the child will get cured within 3 months spontaneously and they doesn't require insulin till there is a disease relapse. But in permanent neonatal diabetes affected children, insulin has to be taken till their lifetime in most of the cases [6-8].

There is presence of two forms of neonatal diabetes. The alteration or mutation of ZAC and HYAMI genes that is present in the chromosome 6q24 locus results in the manifestation of transient neonatal diabetes. The alteration or mutation of KCNJ11 genes encoding the Kir6.2 subunit of ATP sensitive K+ channels, present in the chromosome 6q24 locus results in the manifestation of transient neonatal diabetes.

Individuals having the Permanent Neonatal Diabetes Mellitus because of heterozygous INS pathogenic variants or biallelic deletions of INS will exhibit the features of diabetic ketoacidosis or marked hyperglycemia. Small for gestation age is the common presentation in the newborns. Nine weeks is the usual age of presentation and diagnosis. The presentation will be seen even after the completion of 6 months of age [9-11].

Arriving at a specific genetic diagnosis is considered vital, since it will be useful for the

ISSN 2515-8260 Volume 10, Issue 02, 2023

determination of the type of treatment that has to be administered, thus leading to the good prognosis. Mutation in INS gene is seen as a feature in patients with permanent neonatal diabetes, where good glycaemic control is possible with the effective management through the insulin therapy [13, 14].

Case report

A baby, born out of normal vaginal delivery at term gestation age got affected with this disorder. She was adequate for her age of gestation. The birth weight of the baby was 2,550 grams which was actually normal for the baby. The baby had symptoms of sepsis and then visited the hospital with presenting symptoms. The baby was diagnosed with suspicion of probable of neonatal sepsis and got admitted.

The baby had the presentation of Diabetic Ketoacidosis at the age of 8 weeks. She has high level of random blood glucose (342mg/dl). The investigation of arterial blood gas analysis showed the pH of 6.9 (normal range of 7.35 to 7.45). The baby had undergone the sepsis screening or investigations and it indicate there is no sepsis and hence the infection cause is excluded.

Baby parents also had their investigations done. The blood samples of baby and the parents were subjected to genetic analysis. The genes like KCNJ11, ABCC8 and INS were tested for the mutation and analysed. INS gene in c.314T>G variant with the missense mutation was seen in the baby. The genetic analysis of the parents is found to be negative. Baby was then given insulin as treatment.

After achieving the good glycemic control, the baby was discharged. The glycemic control is considered to be because of both the short and intermediate acting insulin. The course of treatment is maintained for the full period of admission. The growth and development was analysed and found that there is a progression in the treatment period.

Discussion

Among 1-2% of all paediatric diabetic cases, monogenic diabetes occurs. This is a very rare disorder affecting the children. The rarity is because of the low suspicion rate, rare presentation of the clinical features and difficult in doing the investigations or prescribing the investigation that is helpful in the diagnosis of this disorder.

Most of the infants having this disorder will be having the feature of diabetic ketoacidosis. The baby diagnosed in our hospital also has the feature of diabetic ketoacidosis and sepsis at 8 weeks of age. For few weeks after the birth, baby doesn't have the symptoms. The reason for no symptoms or clinical presentation is believed to be presence of residual insulin helping for the normal function in baby.

Previous study showed that molecular cause is considered for the exhibition of neonatal diabetes. They are confirmed by the DNA testing methods [15]. Those molecular tests are of high costs and not easily accessible. Still some laboratories offer this test at high cost.

Permanent neonatal diabetes mellitus will occur because of the mutations seen in the individuals. Those mutations may be autosomal dominant or autosomal recessive or seen as de novo mutation. These mutation leads to disease or disorder. The baby presented also exhibited the genetic alteration in the genetic analysis. The baby parents are found to have normal genes. Thus the mutation in baby is considered as the sporadic mutation. Mutations that are seen in the patients with monogenic diabetes are found to affect the beta cells of pancreas secreting the insulin.

The mutation was seen in the chromosome 11p15 in the locus INS gene. These mutations are dominant. That leads to beta cell death by the process of prevention of proinsulin folding, which in turn results in endoplasmic reticulum stress. Also apoptosis process is found to be responsible. These actions lead to decreased insulin secretion in the body.

Thus, explaining the reason for improvement in glucose levels or glycemic control after the administration of insulin to the affected baby. The change in glucose level is represented by

ISSN 2515-8260 Volume 10, Issue 02, 2023

changes in HbA1c. This type of improvement is also seen in the patients having same gene mutation. But there will be change in the requirement of insulin, some need more insulin, some need few insulin to have the control of glucose.

Absence of autoantibodies confirms the absence of Type 1 diabetes, which actually seen in first 6 months of life. Also complete absence of insulin after certain time, which is characteristic of type 1 diabetes is absent in monogenic diabetes. For normal functioning of baby, insulin is administered exogeneously.

Affected children will show the improvement in growth when the deficiency of insulin gets corrected. The child will have the normal growth as of their peer group i.e, non-diabetic group. The feature is also seen in children having different types of INS gene mutation. The presenting feature may be late onset sepsis along with the features of diabetic ketoacidosis.

Conclusion

A disorder of neonatal diabetes has to be confirmed among the children presenting with features of hyperglycemia and having the glycemic control with insulin therapy. The treatment of the baby will vary according to the mutation in the responsible gene.

The children will have reduced insulin secretion from the pancreatic beta cells if they have the mutation in the INS gene. The insulin treatment to the baby results in good glycemic control. Thus the prognosis is good among them, compared to other gene mutated babies.

References

1. 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 Dec;15(4):1339-41. DOI: 10.4314/ahs.v15i4.37. PMID: 26958039; PMCID: PMC4765401.
2. Sood S, Landreth H, Bustinza J, Chalmers L, Thukaram R. Neonatal Diabetes: Case Report of a 9-Week-Old Presenting Diabetic Ketoacidosis Due to an Activating ABCC8 Gene Mutation. J Investig Med High Impact Case Rep. 2017 Mar 24;5(1):2324709617698718. DOI: 10.1177/2324709617698718. PMID: 28540314; PMCID: PMC5433553.
3. Edghill EL, Flanagan SE, Patch AM, Boustred C, Parrish A, Shields B, et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes. 2008;57(4):1034-1042. DOI: 10.2337/db07-1405. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Babenko AP, Polak M, Cave 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(5):456-466. DOI: 10.1056/NEJMoa 055068. [PubMed] [CrossRef] [Google Scholar]
5. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir 6.2 and permanent neonatal diabetes. N Engl J Med. 2004;350(18):1838-1849. DOI: 10.1056/NEJMoa032922. [PubMed] [CrossRef] [Google Scholar]
6. Sperling MA. ATP-sensitive potassium channels-neonatal diabetes mellitus and beyond. N Engl J Med. 2006;355(5):507-510. DOI: 10.1056/NEJMe068142. [PubMed] [CrossRef] [Google Scholar]
7. Stoy J, Edghill EL, Flanagan SE, Ye H, Paz VP, Pluzhnikov A, et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(38):15040-15044. DOI: 10.1073/pnas.0707291104. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Von Muhlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J

ISSN 2515-8260 Volume 10, Issue 02, 2023

Med. 1995;333(11):704-708. DOI: 10.1056/NEJM199509143331105. [PubMed] [CrossRef] [Google Scholar]

9. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric diabetes. 2009;10(12):33-42. DOI: 10.1111/j.1399-5448.2009.00571.x. [PubMed] [CrossRef] [Google Scholar]
10. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New Engl J Med. 2006;355(5):467-477. DOI: 10.1056/Nejmoa 061759. [PubMed] [CrossRef] [Google Scholar]
11. Garin I, Edghill EL, et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. Proc Natl Acad Sci U S A. 2010 Feb 16;107(7):3105-10. DOI: 10.1073/pnas.0910533107. Epub 2010 Jan 28. PMID: 20133622; PMCID: PMC2840338.
12. Reis AF, Kannengiesser C, Jennane F, Manna TD, Cheurfa N, Oudin C, et al. Two novel mutations in the EIF2AK3 gene in children with Wolcott-Rallison syndrome. Pediatric diabetes. 2011;12(3 Pt 1):187-191. DOI: 10.1111/j.1399-5448.2010. 00679.x. [PubMed] [CrossRef] [Google Scholar]
13. Al-Matary A, Hussain M, Nahari A, Ali J. Permanent neonatal diabetes mellitus. Am J Case Rep. 2012;13:1435. DOI: 10.12659/AJCR.883242. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Iafusco D, Stazi MA, Cotichini R, Cotellessa M, Martinucci ME, Mazzella M, et al. Permanent diabetes mellitus in the first year of life. Diabetologia. 2002;45(6):798-804. DOI: 10.1007/s00125-002-0837-2. [PubMed] [CrossRef] [Google Scholar]
15. Flanagan SE, Patch AM, Mackay DJ, Edghill EL, Gloyn AL, Robinson D, et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes. 2007;56(7):1930-1937. DOI: 10.2337/db07-0043. [PMC free article] [PubMed] [CrossRef] [Google Scholar]