International Journal of Contemporary Pediatrics
Renjish V et al. Int J Contemp Pediatr. 2023 Aug;10(8):1368-1370
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20232265

Case Report

A case of permeant neonatal diabetes with KCNJ11 mutation

Renjish V.[1]*, Carol Sara Cherian[1], Jacob Abraham[1], Shanty Mary Koshy[1], Rajeev Philiip[2]

[1]Department of Paediatrics, [2]Department of Endocrinology, Pushpagiri Institute of Medical Science and Research Centre, Thiruvalla, Kerala, India

Received: 12 June 2023
Accepted: 11 July 2023

***Correspondence:**
Dr. Renjish V.,
E-mail: appurenjish@gmail.com

ABSTRACT

Neonatal diabetes mellitus is considered when there is hyperglycaemia requiring insulin therapy. Phenotypically NDM is classified into three types-transient, permanent and syndromic forms. Permanent NDM-may start in new-born life and is mainly due single gene mutations-KCNJ11 and ABCC8. This mutation is almost 90% manageable with oral sulphonyl ureas. We report a case of Permanent NDM with KCNJ11 mutation who presented in diabetic Ketoacidosis at 4 months of age. Clinical genome sequencing revealed a heterozygous missense variation in exon 1 of the KCNJ11 gene (chr11: g.17387491G>A) that results in the amino acid substitution of cysteine for arginine at codon 201. She was initially treated with insulin for which she had poor glycaemic control. She responded well following the switch over to sulphonylureas with good compliance and has normal development.

Keywords: Neonatal diabetes mellitus, KCNJ11gene, Sulphonylureas

INTRODUCTION

Neonatal hyperglycaemia is common in first 3-5 days of life. It is usually resolves by 2 to 3 days. Neonatal diabetes mellitus is considered when there is hyperglycaemia (blood glucose >250 mg dl) requiring insulin therapy. Neonatal diabetes mellitus is found to be occur 1 in 90,000 to 160,000 of live births.[1] These children may present in severe dehydration, as there is profound glycosuria and may even have ketosis. It is very essential to rule out other causes of neonatal hyperglycaemia like infection, stress, prematurity in infants leading to pancreatic insufficiency, usage of medications like steroid or in some cases iatrogenic administration of glucose containing fluids before considering the diagnosis of neonatal diabetes mellitus.

Phenotypically NDM is classified into three types-transient, permanent and syndromic forms. Transient NDM- onset happens in first week of life but may persist to continue for few weeks or months after which they have spontaneous resolution. Average duration of the disease by 12 weeks. Some of the individual may go on to develope type 1 diabetes mellitus in later life. Permanent NDM-may start in newborn life and is mainly due single gene mutations-KCNJ11 and ABCC8.[5] Among this KCNJ11 mutation cause alteration of sub unit of ATP sensitive K^+ channels of pancreatic beta cells. This leads to dysregulation of insulin secretion. This mutation is almost 90% treatable with oral sulphonyl ureas.[1] Permanent NDM also known to have associations like developmental delay, epilepsy and hypotonia like neurological manifestations. Syndromic forms of NDM-this type are seen in association with several syndromes that may cause beta cell destruction, pancreatic hypoplasia or aplasia. Common syndromes known are Wolcott Rallson syndrome, IDEX syndrome, Fanconi Bickel syndrome etc.

CASE REPORT

A 4-month-old baby presented with poor feeding and activity following a minor illness. On examination she was drowsy and dehydrated with acidotic breathing. At arrival blood glucose was 620 mg dl. Blood gas done showed severe metabolic acidosis (pH-7.139 and HCO_3-

8.9). HbA1c was 15%. She was managed with iv fluids and insulin infusion. She was discharged with insulin on basal bolus regimen and was advised genetic study.

She had irregular follow up and poor compliance with insulin therapy. She later presented at 4 years of age with poor glycaemic control and Hba1c was 17.1%. Blood sugars were managed with insulin infusion and other supportive measures. Clinical exome done detected a heterozygous missense variation in exon 1 of the KCNJ11 gene (chr11:g.17387491G>A; depth: 194x) that results in the amino acid substitution of cysteine for arginine at codon 201 (p.Arg201Cys). Thyroid peroxidase antibody done was negative. Oral glibanclamide was started in low doses along with insulin. Insulin tapered and stopped within 5 months. She showed fair response with treatment of oral sulfonyl ureas within three months. (HBa1c-7.3%, FBS-113 mg dl, PPBS-90 mg dl). Scheduled evaluation is showing child attaining all developmental milestones up to age with no syndromic features or seizures.

DISCUSSION

Permanent NDM typically start before 6 months of age and is mainly caused by KCNJ11/ABCC8 mutation. Among the children with permanent neonatal diabetes, 30-50% patients present in diabetic ketoacidosis.[1] Our child was also in diabetic ketoacidosis at her initial presentation.

Normally in pancreatic beta cell, increased glucose across the GLUT-2 transporter is metabolized by the enzyme glucokinase, and causes increased ATP production. This also leads to closuring of K^+- ATP channel in pancreatic beta cell, which in turn depolarise the cell membrane, activates the calcium channel that will lead to exocytosis of insulin granules.

The gene KCNJ11 encodes for the inner subunit (kir 6.2) of this K^+- ATP channel and ABCC8 encodes for outer subunit (SUR1). Mutations leading to K^+- ATP channel remaining open even at the time of hyperglycaemia. This cause ineffective insulin secretion from pancreatic beta cell. Majority of these mutations are denovo and rarely family history is noticed.[2] Our child had no significant family history. Common signs like polyuria, tachypnea, flu like symptom, tiredness, weakness and dehydration seen in children with neonatal diabetes was also seen in our child during her presentation[3].

As there is presence of K^+- ATP channel in the brain, mutation of this channel also may show features of central nervous system involvement. They may present with ADHD, sleep disturbances, development delay and even seizures. This may be mild delay of development to severe forms like DEND syndrome, which is having development delay and epilepsy along with neonatal diabetes. Other features like autism, learning disability, memory deficits and visuospatial abilities dysfunction which was not noticed in our child.[4]

Initial assessment in neonates may include measurement serum glucose, C- peptide, insulin level, urine and blood ketone level. Genetic testing may be strongly advised as there may be responders to sulphonyl ureas.[5]

Mutation with KCNJ11 and ABCC8 causing permanent NDM may be treated with oral sulphonyl ureas. Around 90-95% these pattern successfully changed from their initial insulin treatment to OHA with good glycemic control.[6] The effect of sulphonyl ureas are due to their effect on mutant K^+- ATP channel in pancreatic beta cell.

Sulphonyl urea bind to SUR1 subunit of K^+- ATP channel, close it independent of Adenosine Triphosphate and cause exocytosis of insulin when there is hyperglycemia. This leads to better glycemic control and prognosis. This makes genetic testing for KCNJ11 important in patients suspected permanent NDM cases. Recent studies showed KCNJ11 mutation patient achieves good glycemic control within 3-6 months after starting sulphonyl ureas.[1]

Glibenclamide is the OHA used in majority of cases of permanent NDM. Other drugs like glipizide, tolbutamide, glimipiride may also be uses but with no superiority among each of them. The risk of hypoglycemia is low when compared to insulin treatment in a 10 year follow up study done.[8]

Initial starting dose of glibenclamide was 0.1 mg/kg/day and increased to 1mg/kg/day gradually. Most common side effects noticed are diarrhoea, nausea, weight loss due to reduced appetite was not noticed in our subject.

In a similar case reported by with mutation of KCNJ11 gene with substitution of C to T at bp (c.601c>t): leading to substitution of amino acid arginine by cytosine at codon 201, R201C, child was successfully shifted to sulphonyl urea from insulin treatment by 4 weeks. It was also a heterozygous mutation and with shift to sulphonyl ureas child showed significant lowering levels of Hba1c.[7]

Neurodevelopmental effects on patients with permanent NDM are favourable if sulphonyl ureas are started earlier. Bownan et al showed better CNS profile in patients with permanent NDM with sulphonyl ureas.[8] Our child is under follow up for growth and neurodevelopment as NDM with KCNJ11 gene mutation are at risk for developing developmental delays and obesity in later life.

CONCLUSION

Patients with suspected permanent NDM should be undergo genetic study to look for KCNJ11 and ABCC8 mutation for the highest benefits from treatment with sulphonylureas. Patients with KCNJ11 mutation can be effectively transferred from their initial insulin treatment

to oral sulphonylureas with good glycaemic control and patient compliance. To tackle glucose level fluctuation mainly seen in neonatal patients with diabetes mellitus and significant reduction in Hba1c levels with increased reduction in diabetes related complication sulphonylureas would be better compared to insulin treatment in people with KCNJ11 mutation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Beltrand J, Busiah K, Vaivre-Douret L, Fauret AL, Berdugo M, Cavé H, Polak M. Neonatal diabetes mellitus. Frontiers Pediatr. 2020:602.
2. Lemelman MB, Letourneau L, Greeley SA. Neonatal diabetes mellitus: an update on diagnosis and management. Clin Perinatol. 2018;45(1):41-59.
3. Letourneau LR, Carmody D, Wroblewski K, Denson AM, Sanyoura M, Naylor RN et al. Diabetes presentation in infancy: high risk of diabetic ketoacidosis. Diabetes Care. 2017;40(10):e147-8.
4. Carmody D, Pastore AN, Landmeier KA, Letourneau LR, Martin R, Hwang JL et al. Patients with KCNJ 11-related diabetes frequently have neuropsychological impairments compared with sibling controls. Diabetic Med. 2016;33(10):1380-6.
5. De Franco E, Flanagan SE, Houghton JA, Allen HL, Mackay DJ, Temple IK et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet. 2015;386(9997):957-63.
6. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6. 2 mutations. N Eng J Med. 2006;355(5):467-77.
7. Madani HA, Fawzy N, Afif A, Abdelghaffar S, Gohar N. Study of Kcnj11 gene mutations in association with monogenic diabetes of infancy and response to sulfonylurea treatment in a cohort study in Egypt. Acta Endocrinologica (Bucharest). 2016;12(2):157.
8. Bowman P, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol. 2018;6(8):637-46.

Cite this article as: Renjish V, Cherian CS, Abraham J, Koshy SM, Philiip R. A case of permeant neonatal diabetes with KCNJ11 mutation. Int J Contemp Pediatr 2023;10:1368-70.