**Case Series**

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# Four Patients with Neonatal Diabetes Mellitus and their Outcomes: A Case Series

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**ABSTRACT**

**Background:** Neonatal diabetes mellitus (NDM) is a severe type of glucose metabolism disorder that appears in the first months of life and mostly presents with symptoms such as dehydration, inability to gain weight, and in extreme cases, ketoacidosis and coma. Strong evidence shows the benefits of early molecular tests that investigate variability in kATP channels such as KCNJ11, ABCC8, INS gene mutations, and 6q24 abnormalities. In the presence of these genomics changes, switching from Insulin treatment toward high-dose oral sulfonylurea can enhance the course of treatment, prognosis, and quality of life.

**Case Report:** In this study, we report four cases of neonatal diabetes with different symptoms who were referred to Shahid Sadoughi Medical Center in Yazd, Iran.

**Conclusion:** The diagnosis and treatment of NDM is a good model for implementing patient-centered and personalized medicine. For all patients with diabetes diagnosed before the 6$^{th}$ month of their age (even the 12$^{th}$ month), genetic testing should be considered.

## Introduction

Neonatal diabetes mellitus (NDM) is a rare type of glucose metabolism disorder that occurs mainly due to a genetic defect in the production or secretion of insulin. It occurs in early life and, conventionally, the onset of hyperglycemia symptoms in the first month of life is known as NDM. However, in recent years, the age limit for NDM diagnosis has been extended to 6 months. The prevalence of NDM is 1:300,000-400,000 live births, and among all cases, it seems that 45% of cases are transient (TNDM), 45% are permanent (PNDM), and 10% of cases occur as a syndrome or with pancreatic aplasia.[1]

Although most of these children have evidence of IUGR and low birth weight due to insulin secretion deficiency, the presentation of this disease can encompass a wide range of symptoms, including failure to thrive, dehydration, and even severe ketoacidosis and coma.[1]

Diagnosing NDM based on clinical symptoms (polyuria and polydipsia) is very challenging due to the high liquid diet of infants and the misplaced reassurance of some doctors. NDM should be considered in children who were born with evidence of IUGR or low birth weight and were not able to gain weight despite receiving enough food (failure to thrive). Early genetic testing is very important in children with diabetes at less than 6 months and has a significant role in determining the course of treatment, and prognosis and evaluating the chance of recurrence in other siblings.[2]

Until the genes responsible for the correct operation of kATP channels were discovered, it was assumed that children with PNDM had insulin-dependent diabetes mellitus. While we now know that many of these patients have a mutation in kATP channels that respond to oral treatment with sulfonylureas, starting oral treatment with high-dose sulfonylurea in these children is associated with improved response to treatment and also improved quality of life.[2]

Neonatal diabetes mellitus (NDM) also is a typical feature of Wolcott-Rallison Syndrome (WRS) with other manifestations like spondyloepiphyseal dysplasia, recurrent hepatic and/or renal dysfunction, hypothyroidism, pancreatic exocrine insufficiency and neutropenia with recurrent infection.[1]

## Case Reports

Here, we report 4 cases with neonatal diabetes mellitus whose clinical descriptions are shown in Table 1.

***Case 1:*** A 2-month-old male infant had been referred to our center due to fever, watery diarrhea, agitation, and vomiting for two days before hospitalization, followed by respiratory distress. The patient was born at term via normal vaginal delivery to a G5L3Ab2 mother with a birth weight of 2500gr. The parents are also relatives. A history of type 2 diabetes was mentioned in the parents' mothers. In the physical examination, the patient's weight was 4 kg (on a 5% percentile line), and he had apparent respiratory distress with a Kussmaul breathing pattern. The preliminary tests show

BS: 681 mg/dl, VBG: Ph: 7.03, Hco3: 3.2, Pco2: 12, Urine Analysis: Glu = +3, Keton = +3, SGOT = 382, SGPT = 216.

Diagnosed with diabetic ketoacidosis, the patient underwent intravenous fluid therapy and intravenous insulin. Antibiotic treatment with cefotaxime and ampicillin was started to treat the expected infection, along with intravenous bicarbonate given to control the severe metabolic acidosis. He also underwent intubation due to severe respiratory distress.

The day after hospitalization, the patient experienced repeated seizures in the form of tonic-clonic movements of the limbs. Cerebral edema was suspected and was treated with intravenous mannitol and anticonvulsant drugs. After getting out of DKA, the patient was disconnected from the ventilator, the intravenous insulin was stopped, and Subcutaneous NPH insulin (2 units in the morning and 1 at night) was started.

**Table 1.** Clinical Description of Four Cases with NDM Referred to Our Center

| Case No. | Age of onset | Presentation | Initial therapy | Genetic testing | Follow up |
|---|---|---|---|---|---|
| 1 | 2 Months | DKA | IV insulin; and then subcutaneous NPH insulin | Wolcott-Rallison Syndrome | Still on INS treatment, BS is under control |
| 2 | 3 Months | vaginal candidiasis | Subcutaneous NPH insulin | ABCC8 mutation | Treatment Switched to sulfonylurea, BS is under control |
| 3 | 1 Months | DKA | IV insulin; and then subcutaneous NPH insulin | not performed due to the high costs | Still on INS treatment, BS is under control |
| 4 | 45 Days | DKA | IV insulin; and then subcutaneous NPH insulin | novel mutation in pancreas development | Not respond to sulfonylurea treatment, Still on INS treatment, BS is under control |

INS= Insulin; BS= Blood Sugerl; NDM: Neonatal Diabetes Mellitus; DKA: Diabetic ketoacidosis

After a few days, the patient was discharged in good general condition and with subcutaneous insulin and Levetiracetam as discharge medication.

In the 2-year follow-up, the patient's blood sugar was under control with subcutaneous insulin, and the patient's anticonvulsant medication was stopped. Also, he had normal development and a normal level of SGPT (=28) AND SGOT (=40). In genetic tests, Wolcott-Rallison Syndrome (WRS) was reported.

***Case 2:*** A 3-month-old female infant patient was referred to our center with a history of vaginal candidiasis from the second month. The patient was born via normal vaginal delivery and had a normal gestational age with a birth weight of 3600 grams. There was also a history of GDM in the patient's mother. She also had a history of using Clotrimazole ointment, but it did not improve her symptoms. In laboratory tests, the blood sugar was 350mg/dl, the blood gas results were normal and in Urine Analysis tests, there was 3+ Glucose. According to these tests, she was diagnosed with NDM and treated with NPH subcutaneous insulin.

In the follow-up, at the age of 18 months, the patient was hospitalized due to fever, pneumonia, and seizures. The patient had a generalized tonic-clonic seizure that lasted for 10 minutes. ABCC8 mutation was reported in the genetic tests. Due to this mutation, NPH insulin was discontinued and sulfonylurea tablets were started (glibenclamide tablets, 5mg, Q12h). In the follow-ups, until the age of 3 years, the patient's diabetes was controlled with glibenclamide tablets, and there were no problems in terms of growth and development.

***Case 3:*** A 2-month-old female infant was admitted to our center for control of her blood sugar. The patient was born by NVD delivery at term to a G2L2 mother with a birth weight of 3 kg. Her family mentioned a history of hospitalization due to fever, diarrhea, dehydration, and respiratory distress one month ago. She was diagnosed with diabetic ketoacidosis and was treated with intravenous fluid therapy and intravenous insulin, after getting out of DKA, subcutaneous NPH insulin was started for the patient. The parents of the patient were also relatives.

In the growth examination, weight = 5700gr (25%), length = 61cm (50%) and head circumference was 38.5cm (5%, it was 33cm at birth). Systemic examinations of the patient were also normal.

The patient was discharged after her blood sugar was controlled with NPH insulin. At the 19-month follow-up, the patient's developmental progress was appropriate for her age. She was still being treated with insulin and her blood sugar was relatively controlled. Genetic tests were not performed due to the high cost.

***Case 4:*** A 12-years and 7-month-old male patient was admitted to our center due to polyuria, polydipsia, and weight loss from

1 month ago. The patient was the second child of a G2L2Ab0 mother as a result of a C-section at 36 weeks gestation with a birth weight of 2400 grams. The parents of the patient were relatives. His parents mentioned the history of hospitalization in infancy due to jaundice and receiving phototherapy. At that time, he had high blood sugar in the tests, but no special action was taken. On the 45$^{th}$ day after birth, the patient was referred to the emergency department complaining of frequent vomiting, poor feeding, and respiratory distress, according to the following tests and with the diagnosis of DKA (BS = 780 mg/dl, VBG: pH = 6.9, HCO3 = 5.9 mEq/L, Urine Analysis: Glucose = +3, Ketone = +3), he was subjected to intravenous fluid therapy and intravenous insulin.

After recovering from DKA, subcutaneous insulin NPH was started for the patient, which was continued for the 7$^{th}$ month of his age. The patient also mentions some learning disorders. At the time of the last hospitalization, in the growth examination, weight: was 38 Kg (25%), and in the laboratory tests, BS = 362 mg/dl, VBG: pH = 7.39, HCO3 = 18.2, PCO2 = 30, Urine Analysis: Glucose = +, Ketone= Negative was reported. With the suspicion of monogenic diabetes, sulfonylurea treatment (glibenclamide tablets, 10mg, Q12h) was started, but no favorable response was observed. In the 4-year follow-up, the patient is still being treated with subcutaneous Basal and Bollus insulin and the patient's diabetes is under control. In the genetic study, a novel mutation in pancreas development was reported.

## Discussion

Neonatal diabetes mellitus is a severe and monogenic type of diabetes with hyperglycemic symptoms that appear in the first months of life which requires the use of insulin, such as dehydration, inability to gain weight, and in severe cases, ketoacidosis and coma.[3] NDM is difficult to diagnose and its incidence rate is also underestimated. Due to the higher chance of neurological complications, neuropsychological defects, and growth retardation, the diagnosis must be made as soon as possible.[4] There is very strong evidence that genetic testing improves the course of treatment and prognosis. The most common genetic causes of neonatal diabetes are mutations in ABCC8 or KCNJ11 genes, which are responsible for encoding potassium channels in pancreatic β cells.[5] Genetic evaluation in children who presented with symptoms of hyperglycemia in the first months of their life is necessary to differentiate neonatal diabetes caused by KATP channel mutation from other forms of insulin-dependent diabetes.[6] These mutations make those infants sensitive to sulfonylurea treatment. Thus, their symptoms and prognosis are greatly improved by switching the treatment from subcutaneous insulin to oral agents.[7] For that reason, the use of sulfonylureas in the treatment of these patients is associated with better control of blood sugar and HbA1c, and reducing the risk of hypoglycemic attacks.[5] The diagnosis and treatment of NDM is a good model for the implementation of personalized medicine.[8]

The onset of symptoms in the majority of patients who were referred to our center was under six months, and the initial symptoms in most of them were diabetic ketoacidosis. Even the second case, which initially presented with vaginal candidiasis, returned to the hospital with symptoms of ketoacidosis at 18 months old, despite the confirmation of NDM diagnosis and the initiation of subcutaneous insulin. This shows that the diagnosis in these patients is obtained with delay or they do not receive proper treatment.

On the other hand, in this study 3 patients had PNDM and one of them had TNDM which relapsed at 12 years and 7 months of age. Among these patients, 3 cases were able to perform the required genetic tests. One case (case 1) had Wolcott-Rallison Syndrome (WRS) in genetic tests. For one of them (case 2) the evidence of ABCC8 mutation was found in those investigations, and the treatment was successfully switched to oral sulfonylureas.

Considering the decisive role of genetic tests in determining the course of therapy and changing the treatment from subcutaneous insulin to oral sulfonylureas. Case 4 had a novel mutation in pancreas development that has not been reported yet and can explain the patient's symptoms.

## Conclusion

In this study, we explored four patients who were referred to our center, each of them presented with hyperglycemic symptoms and high blood sugar in early laboratory testing, and with the diagnoses of diabetes mellitus and mainly diabetic ketoacidosis, they underwent life-saving treatment. Genetic studies are crucial to reach a definite diagnosis in these patients, and it's almost the only way to differentiate neonatal diabetes mellitus from other glucose metabolism disorders. The early diagnosis can play a critical role in determining the treatment path and prognosis of these patients. Approximately 50% of Neonatal diabetes mellitus (NDM) have a mutation in potassium channel function that can insulin therapy switch to oral sulfonylureas therapy with dramatic improvement in glycemic control and quality of life. For all patients with diabetes diagnosed before the 6$^{th}$ month of their age (even the 12$^{th}$ month), Genetic testing should be considered.

## Conflict of Interest

The authors declare that they have no conflicts of interest.

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## Ethical Considerations

The present study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1403.020).

## Author's Contribution

Performing the examination of the patients, major contributors in writing the manuscript, N.M. and M.N; carrying out the genetic experiment, M.M.A; writing- original draft preparation, A.H.Kh. All authors read and approved the final manuscript.

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