Case Report

# Rare association of septic arthritis with neonatal diabetes in a patient with PDX-1 mutation

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## ABSTRACT

We present a 58-day-old male infant with neonatal diabetes and septic arthritis of hip. He was born of a consanguineous marriage at 35 weeks of gestation and was asymptomatic till presentation. Family history revealed his older sibling had suffered from meningitis and a second sibling had neonatal diabetes (died due to an unknown infection). Our patient underwent arthroscopy for septic arthritis and symptoms resolved after antibiotic therapy. Genetic testing was performed for the lipopolysaccharide-responsive beige-like anchor (LRBA) mutation (known to be associated with neonatal diabetes and autoimmune disorders); however, the result revealed a homozygous mutation in PDX-1 gene which is known to cause neonatal diabetes with or without exocrine pancreatic insufficiency. Our case suggests that in neonatal diabetes with atypical infections, genetic causes other than LRBA mutation, like PDX-1 mutation, may be suspected. A genetic diagnosis aids both in treatment and prognostication of neonatal diabetes.

**Key words:** Monogenic diabetes, Neonatal diabetes, PDX-1 mutation, Septic arthritis

Neonatal diabetes has an approximate incidence of 1 in 100,000 live births [1]. The etiology is most commonly monogenic in contrast to autoimmunity which accounts for most cases of type 1 diabetes. The most common genes implicated in neonatal diabetes are ABCC8, KCNJ11, and INS [2]. Homozygous mutation of PDX-1 gene is a rare cause of monogenic diabetes, with or without exocrine pancreatic insufficiency. We present the case of a 2-month-old infant who was diagnosed to have insulin-dependent diabetes with septic arthritis of the hip. To the best of our knowledge, there are no published case reports of an association between these conditions.

## CASE REPORT

We present a 58-day-old male infant with complaints of not gaining weight, increased frequency of urination, dehydration, and refusal to feed. Around the same time, the infant suffered from restricted movements of the left hip. He was born of a 3rd degree consanguineous marriage and delivered through lower segment cesarean section at 35 weeks (in view of premature rupture of membranes with non-progress of labor) with a birth weight of 1.7 kg. The infant had two older sisters. The first sibling developed meningitis at 3 days of life and has a developmental delay. The second was diagnosed to have neonatal diabetes in the 1st month of life and succumbed to some unknown infection in the 2nd month of life (genetic analysis not available).

Examination revealed local tenderness, redness and limited abduction, and external rotation at the left hip due to pain. His blood sugar level was 482 mg/dl (26.8 mmol/l), blood ketones were positive, urine sugar 4+, TSH: 3.99 mIU/ml, venous blood – pH −7.26, and bicarbonate was 16 mmol/l. Radiological investigations revealed effusion (probable septic arthritis) of the left hip.

A diagnosis of neonatal diabetes was made and basal bolus insulin regimen was commenced (glargine 2 units+lispro1/2 units, 3 times a day depending on blood sugar levels). The infant underwent arthroscopy and was treated with antibiotics (linezolid – 90 mg/day, amikacin – 45 mg/day, and meropenem – 180 mg/day) for the same, microscopic examination revealed the material to be purulent (and no organisms were detected on Gram staining and culture failed to show any growth, possibly as the patient had received antibiotics previously). The post-operative course was uneventful and the infant was discharged.

With the above clinical history (neonatal diabetes and atypical infection) along with a history of consanguinity, family history of neonatal diabetes, and atypical infection in the older siblings, a possibility of immunodeficiency in addition to neonatal diabetes

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was considered. For this, genetic analysis was performed, the test revealed that the infant had autosomal recessive neonatal diabetes, subtype PDX-1 (homozygous, located on Chr13:g28498441). Both parents were found to be heterozygous for the same mutation.

The septic arthritis resolved completely after the arthroscopy with no residual disability or recurrences. He is 9 months old now with a weight of 7.5 kg, length of 68 cm and has achieved developmental milestones appropriate for his age. His recent HbA1c was 8.2% and appropriate changes were made to his insulin regime.

## DISCUSSION

Neonatal diabetes is a rare form of diabetes which presents in infants <6 months of age. A genetic diagnosis is warranted since it can predict the transient or permanent nature of the diabetes and can also help in determining the usefulness of oral hypoglycemic agents in the management. Majority of the mutations leading to neonatal diabetes are due to KCNJ11, ABCC8, and INS. When these are ruled out, other causes are usually investigated [3].

Since this patient presented with neonatal diabetes along with septic arthritis, compromised immune response was considered. The most common genetic mutation implicated in infants with neonatal diabetes along with autoimmune disorders is the lipopolysaccharide-responsive beige-like anchor protein mutation [4-6]. However, in our case, genetic analysis revealed that the patient had a mutation in the PDX-1 gene.

PDX1 is a member of the homeodomain family of proteins necessary for pancreatic development. Nicolino *et al*. reported a family where two cousins with permanent neonatal diabetes and no clinical sign of exocrine pancreatic insufficiency had a homozygous missense mutation in *PDX1* (E178G). The E178G mutant protein had reduced transactivation activity, but normal localization, expression level, and chromatin occupancy. They hypothesized that E178G is a hypomorphic mutation, causing the expression of a protein that still retains some residual activity, leading to a milder phenotype [7].

De Franco *et al*. screened a cohort of103 probands with isolated permanent neonatal diabetes in whom ABCC8, KCNJ11, and INS mutations had been excluded. Five cases were found to have a mutation in PDX-1 of which, three had no evidence of exocrine pancreatic insufficiency [8]. In another case report, a small for gestational age male baby with neonatal diabetes was reported to have annular pancreas, gallbladder hypoplasia, and duodenal atresia. On genetic analysis, homozygous mutation p.K163R (c.488A>G) in the PDX1 gene was found. Parents were to be heterozygous for the same mutation [9].

## CONCLUSION

PDX-1 mutation is a known cause of permanent neonatal diabetes. This case highlights the rare association of neonatal diabetes (due to PDX-1 mutation) with septic arthritis of hip in an infant. Genetic analysis when investigating for neonatal diabetes is important since it not only offers a diagnosis and mode of inheritance but also helps in guiding treatment, prognostication, and screening of other known associated disorders.

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