Permanent Neonatal Diabetes (DEND Syndrome)
Sabeen Abid Khan, Arit Parkash and Mohsina Ibrahim

ABSTRACT
DEND syndrome is a very rare syndrome of permanent neonatal diabetes mellitus, with an incidence of < 1/1000,000. It is defined as a triad of developmental delay, epilepsy, and neonatal diabetes. We report the case of a 9-month infant girl who presented with the most severe form of neonatal diabetes mellitus spectrum along with developmental delay and epilepsy. Genetic mutation testing confirmed mutations in KCNJ11 gene encoding the Kir6.2 subunit of the K-ATP channel, which are involved in insulin secretion. The use of oral sulfonylureas in treatment of such patients is showing promising results worldwide. The authors strongly recommend early referral and checking for genetic mutations in all patients of neonatal diabetes mellitus.

Key Words: Neonatal diabetes mellitus. DEND syndrome. Oral sulfonylureas. Epilepsy. Developmental delay.

INTRODUCTION
DEND (developmental delay, epilepsy, neonatal diabetes) syndrome is a very rare syndrome with an incidence of < 1/1000000. It is defined as a triad of developmental delay, epilepsy, and neonatal diabetes. It represents the most severe form of neonatal diabetes mellitus spectrum and is caused by mutations in the K-ATP channel subunits Kir6.2 mainly (encoded by KCNJ11) or SUR1 (sulfonylurea receptor1; encoded by ABCC8) which are involved in insulin secretion.1,2 Intermediate DEND (iDEND) syndrome is a less severe condition in which neonatal diabetes is accompanied by muscle weakness and developmental delay, but not epilepsy. Diabetes manifestations in these patients are similar to that found for patients without neurological features, but the management is more difficult due to marked communication problems and the risk that hypoglycemia can precipitate seizures in patients with epilepsy.

We report a novel case of permanent neonatal diabetes mellitus in association with DEND syndrome.

CASE REPORT
A 9-month female infant weighing 7.9 kgs was referred to our ward with fluctuating blood sugar levels. She was diagnosed as a case of diabetes mellitus at 3 months of age and had been kept on different insulin regimes since then, but her glycemice control had been poor with high blood sugar levels. She was born at 8 months of gestation via C-section, with birth weight of 2100 gms due to maternal hypertension. She did not have any issues at birth and her blood sugar levels were normal. She was born to consanguineous parents although there was no history of diabetes mellitus in the family and her other siblings were all healthy.

At the time of examination, she had a rounded face with no obvious dysmorphisms. Her weight was on 25th centile, height on 3rd centile, and FOC < 3rd centile. Rest of her systemic examination was unremarkable except for hypotonia. Her workup showed random blood sugar level of 385 mg/dl; insulin level was 2.8 U/ml (2 - 25), and her VEP (visual evoked potential) was normal.

At around 6 months of age, she started having recurrent fits for which she was kept on anti-epileptics. At 9 months, her developmental milestones were significantly delayed with no eye contact, babbling, and no neck holding. Due to the findings of significant developmental delay, epilepsy and permanent neonatal diabetes mellitus, she fulfilled all criteria for DEND syndrome.

Her samples for genetic workup were sent to UK, reports showed that she had a heterogeneous p.Q 52 R (P.Gln 52 Arg) mutation in the KCNJ11 gene encoding the Kir6.2 subunit of K-ATP channel. For this reason, she was admitted in hospital for switching to oral sulfonylureas, according to the treatment protocol to which she responded initially. However, she developed fever along with respiratory distress on the third day and her blood sugar levels were also high. Consequently, she was shifted to PICU and needed ventilator support for severe pneumonia, but unfortunately she could not survive her illness.

DISCUSSION
Neonatal diabetes mellitus requiring insulin in the first 6 month of life is a rare entity with an estimated incidence of 1 in 400,000 neonates.3 It can be either transient or permanent. The transient form of the disease, in the
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The majority of cases, resolves by a median of 12 weeks and is generally associated with an abnormality of the imprinted region 6q24. Permanent neonatal diabetes mellitus, on the other hand, needs insulin therapy for life. It may occur as a result of developmental abnormalities of the pancreas (such as pancreatic agenesis or hypoplasia) or defects in the genes encoding the pancreatic β-cell ATP-sensitive potassium channels. DEND syndrome is a severe manifestation of the disease presenting as developmental delay, epilepsy, and neonatal diabetes.

Most newborns with neonatal diabetes mellitus are born with intrauterine growth restriction (IUGR). The degree of IUGR is proportional to the degree of insulin deficiency in utero; this confirms the important role of insulin as a growth factor during gestation. Clinical features of neonatal diabetes mellitus usually occur in the first 3 - 6 months of life, with glycosuria, polyuria, dehydration, failure to thrive, and frank diabetic ketoacidosis; serum levels of insulin and insulin-like growth factor-I are also low. About one-half of patients with neonatal diabetes mellitus have a permanent form that is primarily due to gene mutations related to the ATP-sensitive potassium channel. It has been very recently shown that heterozygous activating mutations in the KCNJ-11 gene, encoding the Kir6.2 subunit of the pancreatic ATP-sensitive K-channel involved in the regulation of insulin secretion cause permanent neonatal diabetes in the majority of cases (30%). Other genetic mutations involved in PNDM include ABCC8 (20%), INS (20%) associated with defect in insulin protein folding and secretion, GCK (20%) associated with homozygous mutation in glucokinase gene, PDX1 (1%) mutation associated with pancreatic agenesis/hypoplasia.

There is a striking genotype-phenotype relationship with specific Kir6.2 mutations being associated with transient neonatal diabetes, permanent neonatal diabetes alone, and (DEND) syndrome.

The physiological importance of K-ATP channels in insulin secretion was established 20 years ago. At sub-stimulatory glucose concentrations, K-efflux through open K-ATP channels maintains the cell membrane at a hyperpolarized potential of around 70 mV, which keeps voltage-gated Ca2+ channels closed. Elevation of the blood glucose concentration increases glucose uptake and metabolism by the cell, producing changes in cytosolic nucleotide concentrations that cause K-ATP channel closure. This leads to a membrane depolarization initiating cell electrical activity and Ca2+ influx, and exocytosis of insulin granules. K-ATP channels are also the target for sulfonylurea drugs, which are widely used to treat type-2 diabetes. These drugs stimulate insulin secretion by binding to, and closing, K-ATP channels. Thus, sulfonylureas bypass cell metabolism but subsequently stimulate the same chain of events as glucose.

As a result, the use of oral sulfonylureas has been studied in patients with permanent neonatal diabetes mellitus with promising results. The high prevalence of Kir6.2 mutations in permanent neonatal diabetes means that all children 6-month of age diagnosed with diabetes should be tested for genetic mutations at diagnosis and assessed for neurological features. Neonatal diabetes mellitus should be referred to Pediatric Endocrinology Unit at the earliest for their comprehensive care. Finding a mutation in KCNJ11 or ABCC8 gene offers the possibility of discontinuing insulin and implementing sulfonylurea therapy while maintaining good glycemic control. Long-term surveillance and reporting of both short-term and long-term outcomes of all patients receiving sulfonylureas is vital.

REFERENCES