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Case Report

Amniocentesis in DEND syndrome and medical termination of pregnancy: a rare disease

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ABSTRACT

An interesting case of DEND Syndrome with history of genetic inheritance and manifestation in the first child. Case is being reported as it is one among the first cases to be confirmed antenatally by Amniocentesis at an obstetric centre in India. Only 60 cases have been reported worldwide as on date as per OMIM database. It has a prevalence of <1: 1000000 worldwide.

Keywords: DEND syndrome, Obstetric surveillance, Amniocentesis, Medical genetics, Genetic screening, MTP services

INTRODUCTION

DEND syndrome is one of the rare genetic variants of neonatal diabetes mellitus characterized by a triad of Developmental delay, epilepsy, and neonatal diabetes (DEND syndrome), which has an adverse outcome if undetected. Outcome and clinical progression depend on early diagnosis and prompt management to prevent Neurological damage. Pancreatic development is normal in this particular variant of neonatal diabetes. Synonym(s): Developmental delay-epilepsy-neonatal diabetes syndrome. Prevalence: <1/1,000,000. This particular variant and its varied expressions have been most reported and extensively studied in Japan.[1]

CASE REPORT

Ms X, 32-year-old lady reported to our centre with history of DEND Syndrome. She had history of their first male child, in a non-consanguineous marriage, with developmental delay, febrile seizures, hypotonia, diabetes mellitus, epilepsy, bedwetting along with psychomotor impairment, mild autistic features (speech delay and echolalia) and hyperactivity along with poor socialization. His NCCT showed bifrontal hyperintensities in white matter and calcification and genetic evaluation with Sanger Sequencing showed heterozygous variant in KCNJ11 gene exon 1 chr11: g.17387407C>T; c. 685G>A, p. Glu229Lys which is known to cause Transient neonatal diabetes mellitus 3 or permanent neonatal diabetes mellitus 2. Parental Sanger sequencing was done and mother was found to have the same variant. Ms.X was diagnosed with diabetes at 2 months POG in her first pregnancy and was started on insulin till delivery. After that she was managed with OHA (Glimepride) and was presently shifted to insulin in ongoing pregnancy with good glycemic control.

Amniocentesis sample was sent for Exome Sequencing, Sanger Sequencing, MCC, QF-PCR for the ongoing pregnancy to rule out index genetic etiology of DEND Syndrome in present gestation or any other associated incidental genetic disease for well-informed clinical decision.

Objectives of the study were

To spread awareness regarding rare diseases and available minimally invasive modalities of accurate diagnosis antenatally and to enable termination of pregnancy if requested by parents after appropriate genetic counselling;

Health education and awareness among clientele.

To enable patients to receive quality healthcare within available resources and reduce burden of healthcare. Importance of Amniocentesis as a simple invaluable tool in Obstetrics for genetic screening and diagnosis. Management of cases as per existing Guidelines within legal framework of PCPNDT Act. Reporting of rare diseases.

Genetic report

Specimen: Amniotic fluid; POG: appx 14-16 weeks; Maternal cell contamination: not detected; QF-PCR for aneuploidy: negative.

Test methodology

Twist exome 2.0 kit, Target exome regions GRCh38 captured using standard hybridization-based target enrichment protocol. The libraries were sequenced at a mean coverage of >90x on the Illumina NovaSeqX Plus sequencing platform. Variant Calling was performed using DRAGEN (Dynamic Read Analysis for GENomics) pipeline, version v4.3.13.

Variant calling and prioritization

All disease variants reported in OMIM and ClinVar.

Incidental findings: None Identified.

Secondary findings: Negative for secondary findings according to ACMG (v3.2).

Table 1: Variant details.

Gene / refseq	Coord (GRch38)	Variant (cDNA)	Exon / intron	Varian t type	Zygosity / inheritance	OMIM Phenotype	Classification (ACMG/AMP)
KCNJ11 / NM_000525 .4	Chr11: 17387407	c685G>A p.Glu229Lys	Exon 1	Missense	Heterozygous AD	Diabetes, permanent neonatal 2, with or without neurologic features; OMIM#618856; DM Transient neonatal 3 OMIM#610582	Pathogenic

Table 2: In silico prediction parameters.

Tool	Effect	Tool	Effect
Bayesdel	Deleterious	Metallr	Deleterious
Revel	Deleterious	Dann	Deleterious
Alphamissense	Deleterious	Sift	Deleterious
Mutation taster	Deleterious		

Table 3: Statistical analysis.

Statistical analysis			
Exome coverage >= 20x	99.17%	Variant read depth	10x
Target genes/regions coverage at 20x	98.85%	Variant allele frequency	50.00%
Exome coverage >= 50x	81.24%	Total reads generated (millions)	55.00%
Target genes/regions coverage at 50x	84.93%	Total reads aligned	99.08%

Variant summary- interpretation

KCNJ11 NM_000525.4: c.685G>A, p. Glu229Lys – Pathogenic

A heterozygous missense variant was detected in the KCNJ11 gene (c.685G>A, p. Glu229Lys). Clinical findings of previous affected child seem to overlap with the manifestations of the condition associated with KCNJ11 gene. It is absent in gnomAD database and has been reported in ClinVar database (VCV000158683.9).

This variant is classified as Pathogenic according to ACMG classification. Further clinical evaluation of the patient will give more insight into the phenotypic overlap.

Variant coverage statistics: Ref allele coverage- G=5; Alt allele coverage- A=5.

OMIM gene and disease association

KCNJ11 (Potassium Inwardly Rectifying Channel Subfamily J Member 11)

Gene: KCNJ11 (Potassium Inwardly Rectifying Channel Subfamily J Member 11) is a Protein Coding gene. Diseases associated with KCNJ11 include Diabetes Mellitus, Transient Neonatal, 3 and Diabetes Mellitus, Permanent Neonatal, 2. Among its related pathways are Inwardly rectifying K+ channels and Cardiac conduction. Gene Ontology (GO) annotations related to this gene include obsolete protein C-terminus binding and voltage-gated potassium channel activity. An important paralog of this gene is KCNJ8.[2]

Diabetes, permanent neonatal 2, with or without neurologic features (OMIM#618856): Permanent neonatal diabetes mellitus-2 (PNDM2) is characterized by onset of insulin-requiring hyperglycemia within the first months of life that requires insulin therapy throughout life. Some patients additionally have marked developmental delay, muscle weakness, and epilepsy. The triad of developmental delay, epilepsy, and neonatal diabetes is known as DEND.[3]

Diabetes mellitus, transient neonatal 3 (OMIM# 610582): Diabetes mellitus, transient neonatal 3 is characterized by Diabetes mellitus, transient neonatal, diabetes mellitus, Gestational diabetes, hyperglycemia, elevated hemoglobin A1c (HbA1c), responsive to oral sulfonylurea, Onset in neonatal period, Onset in 3rd decade of life (in some patients).[4]

DISCUSSION

Clinical description

DEND syndrome is one of the most severe variants of the neonatal diabetes mellitus spectrum. Birth-weight is below the 10th percentile in approximately half of the cases. Patients have hyperglycemia requiring insulin therapy that presents within 12 months of birth. The onset of clinical symptoms is usually before 6 months of age and before 1 month of age in about 1/3rd of the patients. Remission from the hyperglycemia is recorded in about half of the patients (median age 3 years and 3 months, but adequate control may not occur until 5 years old), relapse is seen frequently during puberty. The associated neurological features range from mild to severe developmental delay (psycho-motor and cognitive). ADHD Spectrum, Attention deficit or language disorder (dyslexia) is found in 100% of cases. Patients also present with intractable epilepsy and muscle hypotonia. A less severe, intermediate form has been described known as intermediate DEND syndrome.[5,6]

Etiology

DEND syndrome is caused in most cases by gain of channel function mutations in the KCNJ11 gene (11p15.1), encoding a subunit of the ATP-sensitive potassium (KATP) channel. Mutations also cause permanent neonatal diabetes mellitus (PNDM). 20% of patients with mutations in this gene develop DEND or the intermediate DEND Syndrome. Rare reports of specific mutations in the ABCC8 gene (11p15.1) have been associated with DEND Syndrome.[3,4] Author encourages further reading from OMIM Database which also highlights synopsis of clinical signs in various genetic variants of this rare disease for OMIM #610582, #618856, #601820, #616329 which is elaborately described in a tabular format along with diagnostic criteria which is beyond the scope of discussion in this case report and requires detailed Review of Literature.[4]

Author further recommends detailed reading from all available datasets online from OMIM & ORPHANET™, both of which are updated regularly.

Inheritance: Autosomal Dominant/Autosomal Recessive/ Denovo.

Age of onset: Infancy, neonatal

ICD-10: P70.2
ICD-11: KB60.2Y

Diagnostic methods

DEND syndrome should be suspected when there is onset of diabetes mellitus before 6 months, or before 1 year of age with no pancreatic involvement or no evidence of autoimmune disorder, or with unusual family history and associated neurological complications. The diagnosis is confirmed by genetic testing which should be performed as soon as possible in order to prescribe the appropriate treatment and follow up. Diagnosis should be established before the onset of complications and should not wait for a potential remission of hypoglycemia.

Differential diagnosis

The differential diagnosis includes the less severe intermediate DEND syndrome and other forms of neonatal diabetes mellitus, permanent and/or transient.

Antenatal diagnosis

Non-invasive prenatal testing of fetal genotype can be performed for monogenic diabetes which is highly accurate before the third semester.

Genetic counselling

The mode of inheritance of DEND syndrome is usually dominant (50% of transmitting the disease by an affected couple) and rarely recessive (25% chance of transmitting the disease by an affected couple), however, most diagnosed cases occur from a de novo mutation, in which case, chances of recurrence in siblings are close to zero.

Management and treatment

Treatment should begin as soon as the diagnosis is established using oral sulphonylureas, which act by binding to the regulator SUR1 subunit of the potassium channel, and provides a better metabolic equilibrium than insulin. The clinician should aim to optimize the treatment to the maximum possible dose without causing hypoglycemia (fasting: 70-120 mg/dl - postprandial:100-145 mg/dl) in order to minimize neurological damage. Diet should be carefully balanced (15-18 g/kg/d of carbohydrates) to allow for weight gain and avoid future risk of insulin resistance. Restriction below the RDA in paediatric age group with low birth weight is not beneficial. Blood glucose must be monitored with as little amount of blood as possible (0.3 µl) with glucometer or a continuous glucose monitor.[7,8]

Prognosis

In the neonatal period, the prognosis of the disease is linked to the severity of the symptoms. Rapid diagnosis and treatment with oral hypoglycemic agents sulphonylureas/sulfonylureas; after metabolic control has been restored with insulin, are critical to improve the prognosis and reduce neurological complications. Later in life, the prognosis and complications depend on the glycemic control which further determines appearance of target organ damage. The appearance of target organ involvement could be simultaneous or sequential in long-standing complications of diabetes. It depends on onset of disease with severity and variation in gene expression with varied clinical manifestations and subtypes which are enlisted below for reference of which DEND Syndrome is listed as one of the expressions of the Gene Defect.[7,8]

Diseases List [9]

Disease-causing germline mutation(s) in MODY ORPHA:552.
Disease-causing germline mutation(s) in Isolated permanent neonatal diabetes mellitus ORPHA:99885.
Disease-causing germline mutation(s) in Transient neonatal diabetes mellitus ORPHA:99886.
Disease-causing germline mutation(s) in Autosomal recessive hyperinsulinism due to Kir6.2 deficiency ORPHA:79644.
Disease-causing germline mutation(s) in Autosomal dominant hyperinsulinism due to Kir6.2 deficiency ORPHA:276580.
Disease-causing germline mutation(s) in Diazoxide-resistant focal hyperinsulinism due to Kir6.2 deficiency ORPHA:276603.
Disease-causing germline mutation(s) (gain of function) in Intermediate DEND syndrome ORPHA:99989.
Disease-causing germline mutation(s) (gain of function) in DEND syndrome ORPHA:79134.

Her pregnancy was terminated uneventfully on request and she was discharged on the same day.

CONCLUSION

Genetic Screening of rare diseases in patients looking for answers in unexplained IUD, Mental Illness, Autism Spectrum Disorders, Malignancy, Neurological symptoms, Congenital malformations should not be limited to NT/NB, Dual, Triple or Quadruple Markers, Karyotyping, multiple nonspecific Ultrasounds and other broad tests which are time consuming and offer no answers. Amniocentesis is a quick easy bedside procedure. Availability of WES and Sanger sequencing with good technical support and bedside USG greatly reduces the burden of healthcare in patients with a pre-existing genetic disease in the family.

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Ethical approval: Well informed written consent obtained. PCPNDT Guidelines and laws were adhered to strictly in accordance with the Pre Conception and Pre Natal Diagnostic Testing (PCPNDT) Act, 1994- Govt. of India, the gender of the fetus was not disclosed.

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