Sepiapterin Reductase Deficiency: Diagnostic Challenges in DOPA-Responsive Dystonia

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Case Vignette:

Seven year old male child , firstborn to consanguineous married couple, with normal antenatal, natal and postnatal period, came to our OPD with c/o global developmental delay and febrile seizures at 9 months of age. He started to walk by 2.5 yrs and then had frequent falls. Since 5 years, he had 5 episodes of paroxysmal stiffening with posturing of the right lower limb, lasting for 10-15 minutes and slowly resolving on its own. At present, he can communicate with few words, understands commands, plays in a group, attends special school and takes part in physiotherapy sessions.

Examination reveals hypotonia, just elicitable reflexes with preserved sensory.

Investigations:

Basic blood investigations were normal

Metabolic workup was negative

MRI brain: Normal with the exception of left temporal arachnoid cyst.

Ophthal : normal

ENT: normal

Hence, whole exome sequencing was done in the child & then in the parents i/v/o variants of uncertain significance.

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
SPR **(+)** (ENST00000234454.6)	Exon 1	c.2T>A **(p.Met1?)**	Homozygous	Dystonia, dopa-responsive, due to sepiapterin reductase deficiency (OMIM#612716)	Autosomal recessive	Uncertain Significance **(PM2)**

Analysis for the variant detected by Next Generation Sequencing in the *SPR* gene of index patient, Shameer (Sample ID:8230716)

Name : Jeeya B/Male/38Y Relationship to the index patient : Father Sample ID : 9262798				
Gene Name	**Exon / Intron**	**Variant reported in the index patient**	**Variant detected in family member***	**Clinical condition of family member**
SPR	Exon 1	chr2:g.72887434T>A; c.2T>A (HOM); (p.Met1?)	Present & Heterozygous	NA**

Name : Mubeena J/Female/38Y Relationship to the index patient : Mother Sample ID : 9262861				
Gene Name	**Exon / Intron**	**Variant reported in the index patient**	**Variant detected in family member***	**Clinical condition of family member**
SPR	Exon 1	chr2:g.72887434T>A; c.2T>A (HOM); (p.Met1?)	Present & Heterozygous	NA**

* The variant analysis in Sanger sequencing is based on the *SPR* gene reference sequences ENST00000234454.6 (GRCh38) [1]. The exon number and nucleotide numbers will differ based on the reference file chosen and the database used.

DOPA RESPONSIVE DYSTONIA:

Dopa-responsive dystonia (DRD) or Segawa disease is a rare inherited disease, presents with progressive disabling dystonia at variable ages.

A typical feature is diurnal variation,

Early infantile presentations mimic cerebral palsy. Adult onset presentations include focal dystonia, parkinsonism, psychomotor retardation, seizures, systemic symptoms, and cerebellar dysfunction.

An autosomal dominant heterozygous mutation in the GTP cyclohydrolase I (GCH-1) gene resulting in biopterin deficiency, which is the cofactor for tyrosine hydroxylase (TH) and dopamine deficiency is the most classic molecular pathophysiology.

DRD aselective nigrostriatal dopamine deficiency caused by genetic defects in the dopamine synthetic pathway without nigral cell loss means that DRD is not a neurodegenerative disorder, but a biochemical disorder which should be completely reversed by replacement of the depleted neurochemicals.

Pyruvoyltetrahydropterin synthase (6-PPH4 synthase), sepiapterin reductase (SR), and dihydropteridine reductase (DHPR) (Fig. 1). The defect in GCH-1 activity causes decreased dopamine synthesis, and a low neopterin level.

Dramatic response to levodopa – a characteristic feature.

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