Case Report

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MEPAN Syndrome in an Iranian Child: A Novel Mutation

Fatemeh Arab[1], Mahsa Boogari[2], Najmeh Ahangari[3], Shima Shekari[4], Meisam Babaei[4]*

1. Department of Advanced Technologies, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.
2. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
3. Rare Pediatric Neurological Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
4. Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran.

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Running Title MECR-Related MEPAN with Unusual Manifestations

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ABSTRACT

Mitochondrial Enoyl CoA Reductase Protein-Associated Neurodegeneration (MEPAN) syndrome is an ultra-rare autosomal recessive disorder of mitochondrial fatty acid synthesis, characterized by childhood-onset progressive movement disorder, optic atrophy, and basal ganglia abnormalities. It results from a deficiency of mitochondrial trans-2-enoyl-CoA reductase, an enzyme essential for oxidative phosphorylation and for regulating oxidative stress. We report the first Iranian case of MEPAN syndrome in a 2-year-old boy presenting with developmental delay and several atypical features. Whole-exome sequencing (WES) identified a novel likely pathogenic *MECR* variant. This case underscores the importance of genetic evaluation in children with unexplained developmental delays and expands the clinical spectrum associated with *MECR* mutations.

Introduction

The neurologic disorder related to Mitochondrial Trans-2-Enoyl-CoA Reductase (MECR), known as MEPAN syndrome, is an exceptionally rare autosomal recessive mitochondrial fatty acid synthesis (mtFAS) disorder. It is characterized by a progressive movement disorder that begins in childhood, along with optic atrophy and abnormalities in the basal ganglia. The primary symptoms include early childhood dystonia (15 months–6.5 years) and optic atrophy immediately or even a few years later, which can manifest as impaired visual acuity, impaired speech fluency, and dysarthria. In most cases, intellect remains normal [1]. Human *MECR* encodes mitochondrial trans-2-enoyl-CoA reductase. Mitochondrial trans-2-enoyl-CoA reductase catalyzes the last step of mitochondrial fatty acid synthesis (mtFAS). Mitochondrial fatty acid synthesis is an essential pathway that, in an ACP-dependent manner, plays an important role in endogenous lipoic acid metabolism, mitochondrial translation, tricarboxylic acid (TCA) cycle activity, and iron-sulfur (FeS) cluster biogenesis. mtFAS also participates in accumulating oxidative phosphorylation complexes and regulating oxidative

*** Corresponding Author:**
Meisam Babaei
Address: *Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran.*
E-mail: *babaee1359@gmail.com*

stress. Overall, the mitochondrial fatty acid synthetic pathway reverses the β-oxidation pathway [1-3]. The clinical significance of the *MECR* gene is still not fully understood. In one study, a Purkinje cell-specific gene knockout of the *MECR* gene results in neurodegeneration in animal models [4]. Here we report an Iranian case with a novel genetic variant of the *MECR* gene and unusual neurological symptoms.

Case presentation

A 2-year-old boy from a consanguineous family was referred to Imam Reza Hospital of Bojnourd for further evaluation due to developmental delays in language and motor skills. He was delivered vaginally at term, with a birth head circumference of 34 cm and weight of 3200 g, and required hospitalization as a newborn for jaundice and hypothermia. His family history was notable for epilepsy and mental disorders in a paternal uncle; however, detailed clinical information and genetic status were not available. At the time of referral, the patient had global delay, particularly in the gross motor and verbal domains.

On examination, he did not exhibit syndromic features, but presented with mild generalized ichthyosis, a surgical scar from inguinal hernia repair, and an undescended testicle. His hair was kinky, and he demonstrated psychomotor delays; although attentive, comprehension and response to verbal commands were limited.

Neurological assessment revealed spastic gait and hyperactive deep tendon reflexes (3+). Fundoscopy revealed bilateral optic atrophy with cupping. There was no evidence of pigmentary retinopathy.

MRI of the brain indicated involvement of the globus pallidus, prompting further investigation for Sjögren-Larsson disease. Magnetic resonance spectroscopy (MRS) revealed a decreased N-acetylaspartate-to-creatine (NAA/Cr) ratio. Electrodiagnostic evaluation was normal, leading to the decision to perform whole-exome sequencing (WES) due to suspicion of mitochondrial disorders.

At follow-up (until age 5), the patient experienced a one-week hospitalization for cerebral parenchymal hemorrhage following minor head trauma. The movement disorder (dystonia and tremor) clearly manifested following trivial trauma. He received regular occupational and speech therapy. By age 6, he exhibited dysarthric speech, spastic gait, and mild limb tremors with dystonia. Cognitive assessments indicated blunted attention and hyperactivity. Fundoscopy revealed optic nerve atrophy, and the patient required a brace for ambulation. Based on the prolonged T2 hyperintensity in the globus pallidus, the differential diagnosis included: a) methylmalonic acidemia, b) toxins (carbon monoxide, manganese, cyanide—involves cerebellum too), c) kernicterus (chronic; subthalamic nuclei involved), d) succinate semialdehyde dehydrogenase deficiency, e) guanidinoacetate methyltransferase deficiency, f) isovaleric acidemia, g) pyruvate dehydrogenase (E2) deficiency, h) β-ketothiolase deficiency.

To conduct the genetic analysis, informed consent was signed by the parent. DNA was extracted from the EDTA blood samples using the standard salting-out protocol to ensure high-quality extraction. Whole-exome sequencing (WES) was performed on the proband's DNA using the Illumina NovaSeq 6000 platform, generating 2×100 bp reads with an average coverage of 100× (Macrogen, Korea). In silico bioinformatic analysis revealed c.544C>T, p.Arg182Trp in exon 4 of the *MECR* gene. Co-segregation analysis was performed using Sanger sequencing, which confirmed that both parents were heterozygous carriers of the identified *MECR* variant. Clinical and molecular findings are summarized in Figure 1 and Table 1.

Discussion

Human *MECR* encodes mitochondrial trans-2-enoyl-CoA reductase, the final enzyme in the mitochondrial fatty acid synthesis (mtFAS) pathway. This pathway is essential for multiple mitochondrial functions, including lipoic acid biosynthesis, tricarboxylic acid (TCA) cycle activity, iron–sulfur cluster biogenesis, oxidative phosphorylation complex assembly, and mitochondrial translation. These fundamental roles explain the selective vulnerability of high-energy-demand tissues such as the basal ganglia and optic nerve in *MECR*-related disorders [1,5,6].

MECR-associated disease, also known as MEPAN syndrome, was first described by Heimer et al. in 2016, characterized by childhood-onset dystonia, optic atrophy, and characteristic basal ganglia abnormalities due to biallelic *MECR* variants [1]. Subsequent reports have described a relatively consistent phenotype dominated by movement disorders and visual impairment, while metabolic investigations are often unremarkable. However, *MECR*-related disorders demonstrate significant clinical heterogeneity beyond the classical presentation, including isolated optic neuropathy, adult-onset disease, and even absence of movement disorders, supporting a broad

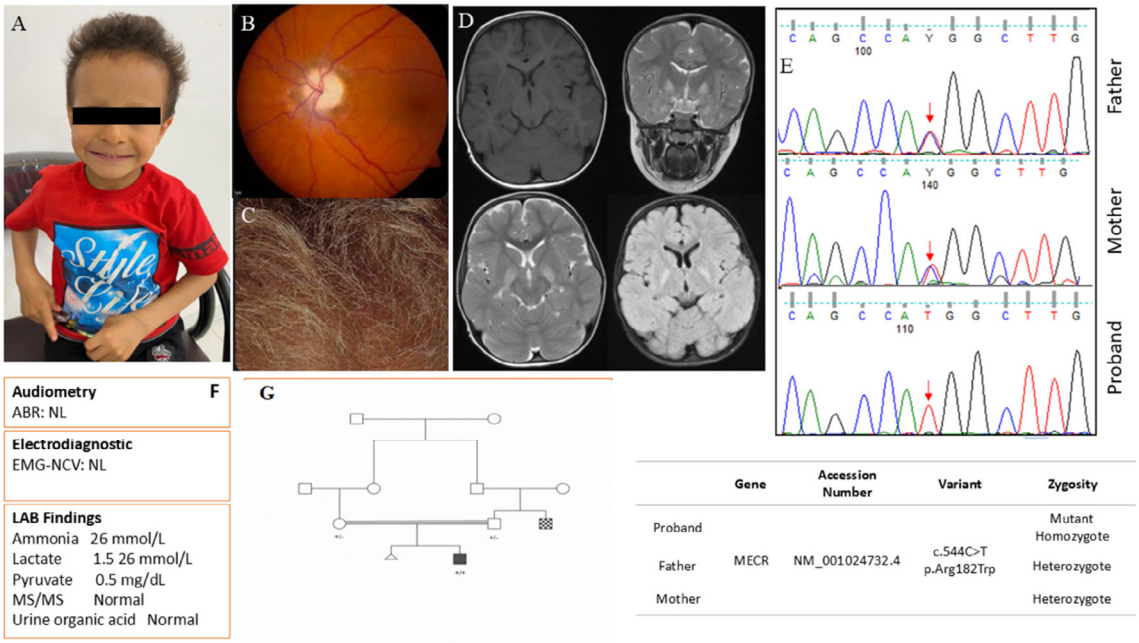

Fig. 1. Clinical and genetic findings in the case. (A) Facial features. (B) Fundoscopic examination revealing optic disc atrophy. (C) Kinky hair. (D) MRI of the brain demonstrated symmetrical hyperintensity in the globus pallidus on both T2-weighted and FLAIR sequences. The follow-up MRI three years later revealed interval development of rarefaction and cystic changes in the previously involved regions. (E) Sanger sequencing confirmed segregation of the *MECR* variant (c.544C>T, p. Arg182Trp) in the family, with both parents identified as heterozygous carriers, supporting autosomal recessive inheritance. **(**F) Auditory brainstem responses (ABR) were within normal limits, indicating preserved peripheral hearing. (G) Pedigree analysis illustrating the inheritance pattern of the *MECR* variant (c.544C>T, p. Arg182Trp) in the family, with affected individuals marked in black. The arrow indicates the proband (IV-2). Variant-altered alleles shown by "+" and wild-type allele shown by "–".

Table 1. Laboratory and diagnostic findings in the case.

Test	Result	Reference Value
Ammonia (mmol/L)	26	<60
Lactate (mmol/L)	1.5	0.6-1.4
Pyruvate (mg/dL)	0.5	0.3-0.7
Mass spectrometry (MS/MS)	Normal	
Urine organic acid	Normal	
Audiometry		
Auditory Brainstem Response (ABR)	Normal	
Electrodiagnostic		
Electromyography (EMG)	Normal	
Nerve Conduction Velocity (NCV)	Normal	

clinical spectrum and limited genotype–phenotype correlation [7].

In our patient, the core features of *MECR*-related neurodegeneration were present, including developmental delay, spastic-dystonic movement disorder, and bilateral optic atrophy with basal ganglia involvement on MRI. However, atypical findings such as ichthyosis and a history of neonatal complications were also observed, which may suggest a broader phenotypic spectrum.

Functional studies further support the role of *MECR* in neuronal survival. Purkinje cell-specific *Mecr* knockout mice develop mitochondrial dysfunction and neurodegeneration, highlighting the critical importance of mtFAS in maintaining neuronal integrity [4].

Conclusion

In conclusion, this case may further expand the clinical spectrum of *MECR*-related disease and highlights the

importance of considering mitochondrial disorders in children with early-onset neurodevelopmental delay and movement disorders.

Ethical Considerations

Ethics approval and consent to participate:

This study was conducted in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of North Khorasan University of Medical Sciences (Ethics Code: IR.NKUMS.REC.1404.035). Written informed consent for participation and genetic testing was obtained from the patient's legal guardians.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interests

The authors have no conflict of interest to declare.

Author Contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Meisam Babaei, Fatemeh Arab. The first draft of the manuscript was written by Mahsa Boogari, Shima Shekari and Najmeh Ahangari. All authors read and approved the final manuscript.

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