Novel SEPSECS Pathogenic Variants Featuring Unusual Phenotype of Complex Movement Disorder With Thin Corpus Callosum

A Case Report

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Abstract

Objectives
To report a novel association between pathogenic variants in the SEPSECS gene and complex movement disorder with thin corpus callosum (TCC).

Methods
Clinical exome sequencing was performed in an adult patient with a genetically unsolved neurodegenerative disorder. The main clinical, neuroimaging, and genetic data were described.

Results
The c.865C > T (p.P289S) and c.1297T > C (p.Y433H) missense variants in SEPSECS (NM_016955.3) were discovered.

Discussion
This case represents a novel form of early-onset pyramidal syndrome with optic nerve hypoplasia, which slowly evolved to extrapyramidal syndrome featuring dystonia-parkinsonism, associated with TCC, caused by SEPSECS pathogenic variants. This form enlarges the group of the so-called pyramidal-extrapyramidal syndromes, as well as complex hereditary spastic paraparesis with TCC.
Selenoprotein deficiency is caused by mutations in SECISBP2, SEPSECS, and TRU-TCA1-1, which are 3 crucial components of the selenocysteine (Sec) amino acid insertion pathway into at least 25 human selenoproteins. SEPSECS, located at 4p15.2, consists of 12 exons and codes for the Sep (O-phosphoserine) tRNA:Sec tRNA synthase, a 501-amino acid protein that catalyzes the last step in the conversion of Sep-tRNA to Sec-tRNA. We describe a novel phenotype caused by recessive SEPSECS pathogenic variants.

Case Description

A 48-year-old man, the offspring of nonconsanguineous parents, had a history of normal birth and development in the first year of life. At age 13 months, he manifested head titubation and ocular nystagmus. He started walking independently at age 14 months and manifested toe walking from the age of 2 years. Language developed normally. Investigations performed over years at several Italian centers included routine biochemistry, metabolic screening, neurophysiology tests, and karyotype that were all unremarkable except for selective IgA deficiency. A brain CT performed at age 18 years indicated mild atrophy of frontal lobes. An ophthalmologic examination documented bilateral optic nerve hypoplasia. Given the constellation of his signs, a diagnosis of spastic paraparesis with nystagmus was considered. Over time, his motor abilities slowly worsened, although he was able to complete high school and work as a school assistant until beginning of the Covid-19 pandemic. Brain MRI performed at age 41 years showed mildly increased frontotemporal subarachnoid spaces and thin corpus callosum (TCC) (Figure). At our first neurologic examination at age 48 years (Video 1), he exhibited normal comprehension with mild bradyphrenia. His language was understandable though dysarthric. A rotatory and horizontal subcontinuous ocular nystagmus was evident, as well as microcephaly (occipito-frontal circumference 52 cm). Bradykinesia and mild dystonic cervical and feet posturing were evident, as well as mild extrapyramidal rigidity at the upper limb. Deep tendon reflexes were abolished at lower limbs. He was able to walk autonomously with mild wide-based and festinating gait. Neurophysiologic studies showed abnormal motor-evoked and visual-evoked potentials. Nerve conduction studies and electroretinogram were normal.

The study was conducted in accordance with the Declaration of Helsinki. The patient signed consent forms for genetic analysis and for data publication.

Results

Clinical exome sequencing discovered compound heterozygous c.865C > T (p.P289S) and c.1297T > C (p.Y433H) missense variants in SEPSECS (NM_016955.3). The 2 variants were both absent in controls (i.e., Exome Sequencing Project, 1000 Genomes Project, Exome Aggregation Consortium) (PM2 criteria) and were in trans because they were inherited from heterozygous parents (PM4 criteria). In silico prediction programs supported a deleterious effect on the gene product (25 of 25 and 24 of 25 programs on VarSome [varsome.com/] indicate the 2 variants as pathogenic, respectively) (PP3 criteria); in addition, patient’s phenotype is highly specific for a disease with a single genetic etiology (PP4 criteria), and missense variants are a common mechanism of disease in SEPSECS-related disorders (PP2 criteria). According to the abovementioned American College of Medical Genetics criteria, the 2 variants were classified as likely pathogenic (V).

Discussion

Selenoproteins are involved in several biological processes as antioxidant defense, regulation of gene expression, control of extrapyramidal rigidity at the upper limb. Deep tendon reflexes were abolished at lower limbs. He was able to walk autonomously with mild wide-based and festinating gait. Neurophysiologic studies showed abnormal motor-evoked and visual-evoked potentials. Nerve conduction studies and electroretinogram were normal.

All procedures followed were in line with the journal’s ethics policy, and the subject gave consent to be videoed for publication both in print and online.

Discussion

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Figure Brain Magnetic Resonance Imaging, Sagittal T2-Weighted and Axial T2-FLAIR Images, Performed at Age 41 Years

Mildly increased frontotemporal subarachnoid spaces (A) and thin corpus callosum (B), with no basal ganglia (A), white matter (A), cerebellum, and midbrain anomalies (B).
protein folding, and metabolism of thyroid hormones. Systemic selenoprotein deficiencies due to SECISBP2 and TRUC TCA1-1 recessive pathogenic variants are characterized by multiorgan defects, including abnormal thyroid hormone metabolism, myopathy, hearing loss, and male infertility. Pathogenic variants in SEPSECS cause pontocerebellar hypoplasia (PCH) type 2D (PCH2D, OMIM #613811). PCH are rare prenatal-onset neurodegenerative disorders characterized by progressive microcephaly, spasticity, profound mental impairment, and progressive pontocerebellar (and neocortical) atrophy. Dyskinetic movement disorder characterizes the subgroup type 2. PCH2D may span axonal neuropathy, myopathy, epilepsy or epileptic encephalopathy featuring West syndrome, optic nerve hypoplasia, and high blood lactate. In addition, milder neurodegenerative phenotype characterized by early-onset ataxia with microcephaly and progressive cerebellar atrophy has been described in 3 patients.

Our patient had a unique combination of pyramidal-extrapyramidal syndrome and optic nerve hypoplasia with TCC without basal ganglia, cerebellum, and midbrain anomalies. Pyramidal features clinically predominated in the first 2 decades, while extrapyramidal symptoms appeared over disease’s course in the form of dystonia-parkinsonism with a very slow degenerative course.

Parkinsonian-pyramidal syndromes include neurodegenerative diseases as complex hereditary spastic paraparesis (HSP) (e.g., SPG10, SPG11, SPG15), young-onset parkinsonism, neurodegeneration with brain iron accumulation, primary familial neonatal-onset form, and dementia with Lewy bodies. Pyramidal features clinically predominated in the first 2 decades, while extrapyramidal symptoms appeared over disease’s course in the form of dystonia-parkinsonism with a very slow degenerative course.

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