

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

A Case Report

Francesco Nicita, MD, PhD, Lorena Travaglini, PhD, Francesco Bombelli, MD, Michele Tosi, MD, Stefano Pro, MD, Enrico Bertini, MD, and Adele D'Amico, MD, PhD

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Correspondence

Dr. Nicita
francesco.nicita@opbg.net

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_016,955.3) 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.

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From the Genetics and Rare Diseases Research Division (N.D.F., L.T., M.T., E.B., A.D.A.), Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS; Studio Neurologico Laterano (F.B.); and Neurophysiology Unit (S.P.), Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.

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Selenoprotein deficiency is caused by mutations in *SECISBP2*, *SEPSECS*, and *TRU-TCAI-1*, which are 3 crucial components of the selenocysteine (Sec) amino acid insertion pathway into at least 25 human selenoproteins.¹ *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.

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.

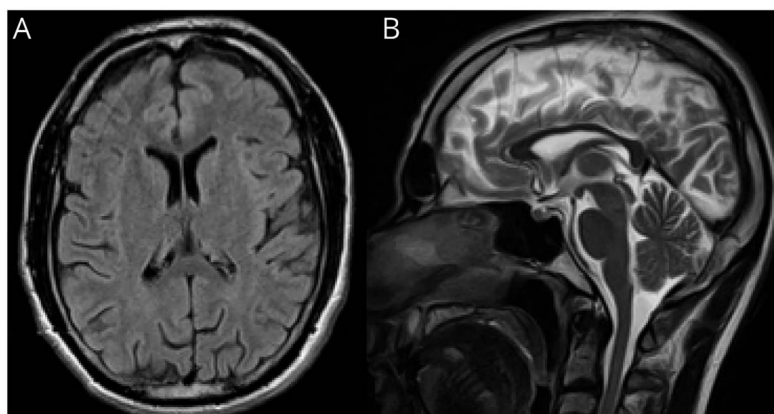
Results

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,² 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

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.¹ Systemic selenoproteins deficiencies due to *SECISBP2* and *TRU-TCA1-1* recessive pathogenic variants are characterized by multiorgan defects, including abnormal thyroid hormone metabolism, myopathy, hearing loss, and male infertility.¹ 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.³⁻⁵ In addition, milder neurodegenerative phenotype characterized by early-onset ataxia with microcephaly and progressive cerebellar atrophy has been described in 3 patients.^{6,7}

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 brain calcifications, inborn errors of metabolism (e.g., mitochondrial diseases, Wilson disease, neuronal ceroid lipofuscinosis, manganese transport disorders, Gaucher disease type 3, Niemann-Pick type C, GM1 gangliosidosis type 3).⁸ Most of these conditions have biochemical and/or neuroimaging diagnostic clues, which in our case were limited to TCC, a feature observed in few HSP. Association with optic neuropathy is mainly confined to mitochondrial diseases. In this regard, shared features between mitochondrial and selenoprotein disorders may be related to the role of selenoproteins in the maintenance of redox potential, regulation of redox-sensitive biochemical pathways, and protection from oxidative damage.¹ Other authors suggested that cells with high mitochondrial activity may be affected by *SEPSECS* deficiency because mitochondria are one of the main sources of cellular reactive oxygen species.³ In conclusion, we describe a patient with early-onset and slowly progressive complex movement disorder caused by novel biallelic *SEPSECS* pathogenic variants. Our case increases the clinical, mutational, and neuroimaging spectrum of *SEPSECS*-related phenotypes. An analysis of the few published pathogenic *SEPSECS* variants indicated that different types of mutations are spread along the gene, thus not clarifying the genotype-phenotype correlations.³⁻⁷ Reasons for phenotypic variability remain to be explained.

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Appendix Authors

Name	Location	Contribution
Francesco Nicita, MD, PhD	Genetics and Rare Diseases Research Division, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Lorena Travaglini, PhD	Genetics and Rare Diseases Research Division, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Francesco Bombelli, MD	Studio Neurologico Laterano, Rome, Italy	Drafting/revision of the article for content, including medical writing for content, and major role in the acquisition of data
Michele Tosi, MD	Genetics and Rare Diseases Research Division, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Stefano Pro, MD	Neurophysiology Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content, and analysis or interpretation of data
Enrico Bertini, MD	Genetics and Rare Diseases Research Division, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content; and analysis or interpretation of data
Adele D'Amico, MD, PhD	Genetics and Rare Diseases Research Division, Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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