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Two Siblings with Cerebellar Ataxia, Mental Retardation, and Disequilibrium Syndrome 4 and a Novel Variant of *ATP8A2*

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Cerebellar ataxia, mental retardation, and disequilibrium syndrome 4 (CAMRQ4) is early onset neuromotor disorder and intellectual disabilities caused by variants of *ATP8A2*. We report sibling cases and systematically analyze previous literature to increase our understanding of CAMRQ4. Japanese siblings presented with athetotic movements at 1 and 2 months of age. They also had ptosis, ophthalmoplegia, feeding difficulty, hypotonia, and severely delayed development. One patient had retinal degeneration and optic atrophy. Flattening of the auditory brainstem responses and areflexia developed. At the last follow-up, neither patient could sit or achieve head control, although some nonverbal communication was preserved. Whole exome sequencing revealed compound heterozygous variants of *ATP8A2*: NM_016529.6:c.[1741C>T];[2158C>T] p.[(Arg581*)];[(Arg720*)]. The p.(Arg581*) variant has been reported, while the variant p.(Arg720*) was novel. The symptoms did not progress in the early period of development, which makes it difficult to distinguish from dyskinetic cerebral palsy, particularly in solitary cases. However, visual and hearing impairments associated with involuntary movements and severe developmental delay may be a clue to suspect CAMRQ4.

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Introduction

The asymmetric distribution of lipids across the lipid bilayer is a characteristic feature of cell membranes, where phosphatidylcholine, sphingomyelin, and glycolipids are enriched on the external or exoplasmic leaflet of the membrane and phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol are primarily confined to the cytoplasmic leaflet (Andersen et al. 2016). P4-ATPases are a subfamily of P-type ATPases that actively transport specific phospholipids from the exoplasmic to the cytoplasmic leaflet of the membrane to generate and maintain asymmetry of membrane lipids, which is essential for a variety of cellular processes, such as vesicle budding and trafficking, cell signaling, blood coagulation, apoptosis, bile and cholesterol homeostasis, and neuron survival (Andersen et al. 2016). Among the 14 P4-ATPsases (flippases), only three (*ATP8A2*, *ATP8B1,* and *ATP11A*) have been associated with human disease (Andersen et al. 2016; Segawa et al. 2021).

The *ATP8A2* gene is mainly expressed in the cerebrum, cerebellum, spinal cord, retina, and testis, where ATP8A2 is involved in the transport of aminophospholipids

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toward the cytoplasmic leaflet in these tissues (Coleman et al. 2009; Cacciagli et al. 2010; Zhu et al. 2012). *ATP8A2* variants were initially identified in a family with a clinical phenotype of cerebellar ataxia, mental retardation, and disequilibrium (CAMRQ) syndrome (Onat et al. 2013). The genes causing CAMRQ syndrome are diverse, and include *VLDLR* (CAMRQ1; MIM: 224050), *WDR81* (CAMRQ2; MIM: 610185), and *CA8* (CAMRQ3; MIM: 613227). Recently, CAMRQ syndrome caused by *ATP8A2* variants was named CAMRQ4 (MIM: 615268) (Onat et al. 2013; Guissart et al. 2020).

Here, we report clinical and genetic analyses of additional Japanese siblings with CAMRQ4, and reviewed previous papers.

Case Presentation

Patient 1

The patient was a 28-year-old woman born by Cesarean delivery after a full-term pregnancy and without asphyxia to healthy non-consanguineous Japanese parents. Her birth body weight was 2,786 g [–0.5 standard deviation (SD)], body length was 47.3 cm (–0.5 SD), and occipitofrontal circumference (OFC) was 35.1 cm (+1.6 SD). She was noticed to have hypotonia and feeding difficulty soon after birth. She was referred to our hospital at the age of 6 months, when she had hypotonic, dyskinetic quadriplegia, bilateral blepharoptosis, no visual pursuit, and delayed development without head control or rolling. There were no remarkable findings in terms of routine biochemical studies, serum analysis of amino acids, lactate/pyruvate levels, or cerebrospinal fluid (CSF) 5-hydroxyindole acetic acid and homovanillic acid (HVA) levels. Gas chromatograph-mass spectrometry (GC/MS) of urine was also unremarkable. Brain magnetic resonance imaging (MRI) at 19 months old showed mildly delayed myelination. Atrophy of the cerebellum was unremarkable (Fig. 1A, B). The auditory brainstem responses (ABR) showed poor wave form differentiation, and subsequently showed a flat pattern of all I-V wave forms. An ophthalmological study was unremarkable. The visual evoked responses (VEP) were normal, but the short-latency somatosensory evoked potentials (SSEPs) showed reduced cortical responses. Because deep tendon reflexes were absent, a biopsy of the quadriceps muscle was performed at the age of 3 years under the suspicion of peripheral nerve neuropathy or mitochondrial disease. The biopsy showed variation in fiber size but a normal appearance of the intramuscular nerve twigs (Fig. 1E, F). G-banding analysis and fluorescence *in situ* hybridization for Angelman syndrome were also normal. Electroencephalography (EEG) was normal at 7 years old. She had nevus pigmentosus on the lower extremities.

She was undergoing outpatient rehabilitation. At the age of 17 years, she had no meaningful words, but showed vague responses to her surroundings. She could take special food orally and make some facial expressions. She could turn over and do supported standing for a few minutes without head control. While seated with a chest belt, she could hold toys for a while. Her patellar and Achilles tendon reflexes were absent. Doll's eye responses and visual responses were also negative. She had bilateral ptosis. Pes planovalgus and dyskinetic movement of the tongue, face and extremities were observed continuously. The spontaneous Babinski sign was also positive.

After graduating from a special needs senior high school, she has been attending a care house daily.

Patient 2

This 25-year-old younger brother was born by Cesarean delivery after a full-term pregnancy without asphyxia. His birth body weight was 2,578 g (–1.0 SD), body length was 46.5 cm (–1.2 SD), and OFC was 34 cm (+0.5 SD). Like his sister, he was noticed to have athetotic movement at 2 months of age. Delayed development was also evident. At the age of 7 months, the CSF HVA, 5HIAA, lactate, and pyruvate levels were unremarkable. ABR showed equivocal wave forms (Fig. 1G-I). Prolonged febrile and afebrile convulsions occurred twice during infancy. Valproic acid (VPA) was started for suspected epilepsy. GC/MS of urine, tandem mass spectrometry, and multiplex ligation-dependent probe amplification (MLPA) of the telomeres at the age of 11 years were unremarkable. Brain MRI at 6 years of age showed mildly dilated lateral ventricles without cerebellar atrophy (Fig. 1C, D). Magnetic resonance spectroscopy of the basal ganglia was normal. An ophthalmological study at the age of 6 years revealed retinal degeneration and optic nerve atrophy. Repeat ABR showed a flat pattern at the age of 8 years (Fig. 1J) and SSEP showed flattened cortical responses at 11 years (Fig. 1K). Neurological examination at the age of 11 showed no head control, sitting, or meaningful words. He had bilateral ptosis. Visual acuity was not determined. Doll's eye responses were negative. The response to pain stimuli was reduced. He could roll over. Dystonia and athetosis of the extremities and trunk, profound variable hypotonia, and bilateral planovalgus were evident. The deep tendon reflexes were all absent, as was the Babinski reflex. While seated with a chest belt, he could play with toys and watch television. Drooling was remarkable, but he could take special food orally. A high arched palate and a misaligned tooth were noted. He enjoyed listening to music. An EEG at 11 years showed no epileptic discharges, but a severely disorganized waking background was noted.

Genetic testing

To establish a molecular diagnosis, we conducted family-based whole-exome sequencing, as previously described (Takezawa et al. 2018; Takayama et al. 2021). The patients and their family provided informed consent for next-generation sequencing and publication of this case report. The study was approved by the ethics review boards of Miyagi Children's Hospital and Tohoku University Hospital. We identified compound heterozygous variants of *ATP8A2*,

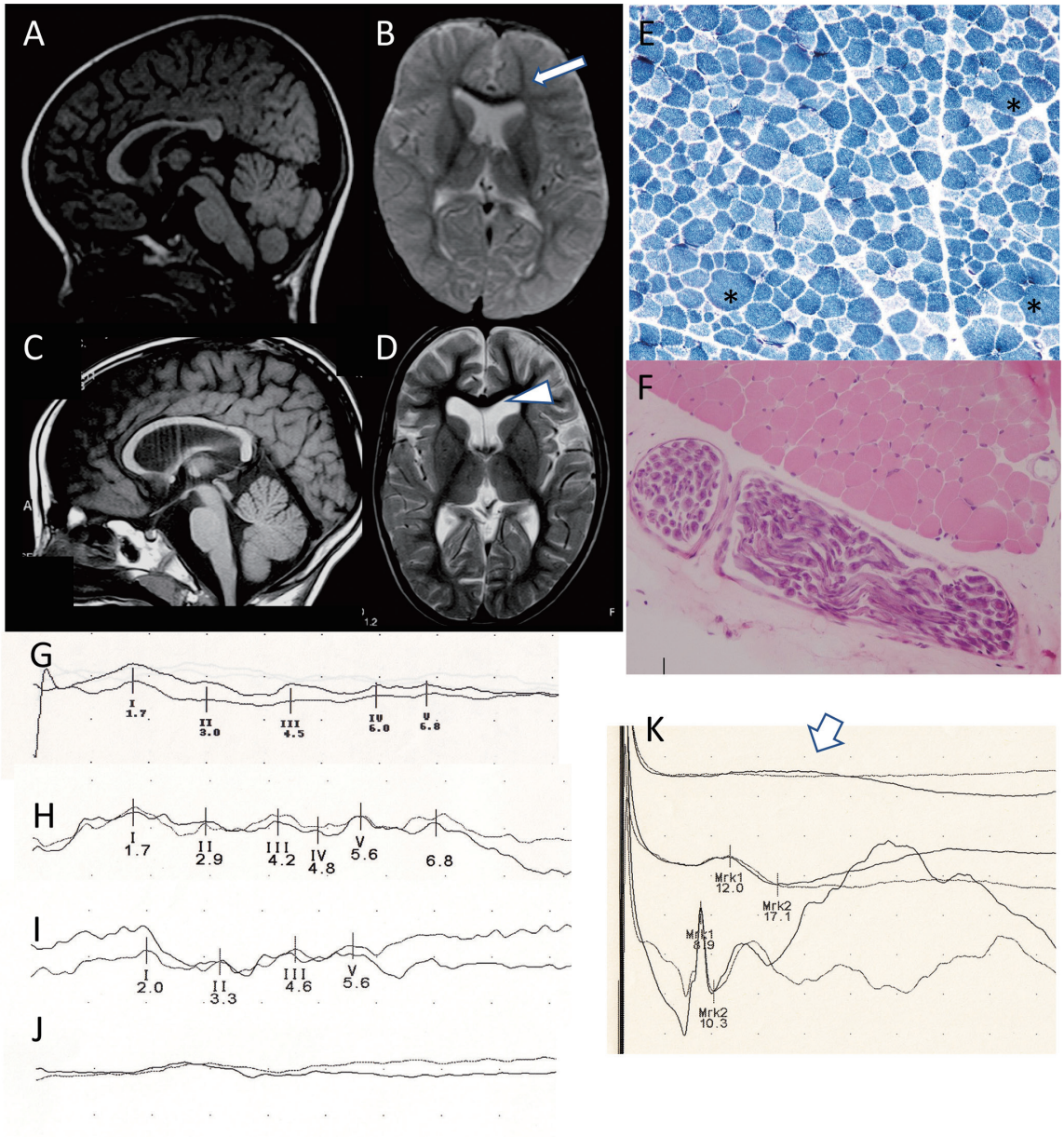

Fig. 1. Brain magnetic resonance imaging (MRI) of patients 1 (A, B) and 2 (C, D), muscle biopsy of patient 1 (E, F), and electrophysiological study of patient 2 (G-K).
The brain MRI of patient 1 at 19 months old (A, B) showed delayed myelination (arrow). Cerebellar atrophy was not observed. The brain MRI of patient 2 at the age of 6 years (C, D) showed no cerebellar or cortical atrophy but had mildly dilated lateral ventricles (arrowhead) (A, C: T1-weighted images, and B, D: T2-weighted images). A quadriceps biopsy showed variation in fiber size with some hypertrophic fibers (asterisks) on NADH-TR staining (E). The intramuscular nerve twig showed normal appearances on hematoxylin and eosin staining (F). Auditory brainstem responses of patient 2 at G) 1, H) 3, I) 7, and J) 8 years showed progressive flattening. The short latency somatosensory evoked potential at 11 years of age showed flattening of the cortical responses (arrow) (left median nerve stimulation) (K).

NM_016529.6:c.[1741C>T];[2158C>T] p.[(Arg581*)];[(Arg720*)], which were confirmed by Sanger sequencing. No other pathogenic variants were observed. The maternal variant p.(Arg581*) has already been reported (Alsahli et al. 2018), while the paternal variant p.(Arg720*) was novel. Both variants are considered pathogenic based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al. 2015): PVS1+PS1+PM2+PM3+PP3+PP4+PP5 for p.Arg581* and PVS1+PM2+PM3+PP3+PP4+PP5 for p.Arg720* (PVS, pathogenic very strong; PS, pathogenic strong; PM, pathogenic moderate; PP, pathogenic supporting).

Discussion

Both patients presented severe intellectual disability, dyskinetic quadriplegia, hypotonia, ophthalmoplegia, ptosis, visual and auditory disturbance. The absence of deep tendon reflexes suggested peripheral nerve involvement,

although electrophysiological study was not able due to parents' decline. Thirty-three patients with CAMRQ4 have been described from 25 families (Table 1). These patients have consistent early onset neuromotor disorders and intellectual disabilities (Cacciagli et al. 2010; Onat et al. 2013; Martin-Hernandez et al. 2016; Quintas et al. 2017; Alsahli et al. 2018; McMillan et al. 2018; Guissart et al. 2020; Mohamadian et al. 2020; Heidari et al. 2021; Damasio et al. 2021). As shown in the Table 1, 80-90% of these patients were non-ambulatory and hypotonic, and presented with feeding difficulties and involuntary movements (Table 1). Optic atrophy, ophthalmoplegia, nystagmus, strabismus, and ptosis were observed in 50% of the patients (Table 1). A recent report demonstrated minor anomalies, such as an elongated face, high arched palate, dental misalignment, and micrognathia. Notable progressive changes in ABR

Table 1. Clincal summary of present patients and genetically determined 33 cases of CAMRQ4.

	Pt 1	Pt 2	Heideri et al. 2021 N = 3 (3 family)*	Damasio et al. 2021 N = 2 (1 family)	Mohamadian et al. 2020 N = 3 (1 family)	Guissart et al. 2020 N = 6 (5 family)	McMillan et al. 2018 N = 9 (7 family)	Alsahli et al. 2018 N =5 (3 family)	Quintas et al. 2017 N = 1	Martin-Hernandez et al. 2016 N = 2 (2 family)	Onat et al. 2013 N = 1	Cacciagili et al. 2010 N = 1	Summary of reviously genetically determined cases (N = 33)
Age at onset (months)	1	2	6-12	2-4	0	0-24	0-6	2-4	6	0-1	ND	1	
Age at last investigation (years)	28	25	6/8/6	18/26	9/15/17	2-28	2.5-28	4-14	11	7/5	27	3	
Developmental delay	Yes	Yes	3/3	2/2	3/3	6/6	9/9	5/5	1	2/2	1	1	33/33 (100%)
Intellectual disability	Yes	Yes	3/3	0/2	3/3	4/6	9/9	5/5	1	2/2	1	1	29/33 (88%)
No meaningful words	Yes	Yes	1/3	0/2	0/3	2/6	9/9	5/5	0	1/2	0	0	18/33 (55%)
Few words	No	No	2/3	ND	ND	4/6	0/9	0/5	ND	1/2	ND	1	8/26 (31%)
Dysarthric speech	No	No	ND	2/2	3/3	4/6	ND	5/5	1	ND	1	ND	16/18 (89%)
Non-ambulatory	Yes	Yes	3/3	0/2	3/3	4/6	9/9	5/5	1	2/2	1	1	29/33 (88%)
Hypotonia	Yes	Yes	2/3	2/2	3/3	4/6	9/9	5/5	ND	2/2	0	1	28/32 (88%)
Muscle weakness	Yes	Yes	1/3	ND	ND	3/6	5/6	3/3	ND	2/2	0	ND	14/21 (67%)
Seizures	No	Yes	2/3	ND	ND	3/6	2/9	ND	ND	0/2	1	ND	8/21 (38%)
Chorea or choreoathetosis	Yes	Yes	3/3	0/2	ND	2/5	9/9	5/5	1	2/2	ND	ND	22/27 (81%)
Dystonia	Yes	Yes	3/3	2/2	ND	3/6	3/9	ND	ND	1/2	ND	ND	13/22 (59%)
Facial dyskinesia	Yes	Yes	3/3	ND	ND	1/5	0/9	ND	ND	2/2	ND	ND	6/19 (32%)
Tremor	No	No	0/3	ND	ND	3/5	ND	ND	ND	ND	1	ND	4/9 (44%)
Head titubation	No	No	3/3	ND	ND	3/4	ND	ND	ND	ND	ND	ND	6/7 (86%)
No siting, no head control	Yes	Yes	2/3	0/2	3/3	ND	7/9	5/5	ND	2/2	ND	1	20/30 (73%)
Ataxia (including astasia-abasia)	Yes	Yes	3/3	2/2	3/3	3/4	ND	5/5	ND	2/2	1	ND	17/20 (85%)
Brisk lower leg reflexes	No	No	0/3	2/2	0/3	3/6	ND	ND	ND	ND	1	ND	6/15 (40%)
Reduced lower leg reflexes	Yes	Yes	1/3	ND	3/3	2/6	ND	2/3	ND	ND	0	ND	8/16 (50%)
Babinski ref/extensor plantar response	No	No	3/3	0/2	ND	4/5	ND	ND	ND	ND	ND	ND	7/10 (70%)
Spasticity	No	No	ND	2/2	ND	ND	ND	ND	ND	ND	ND	ND	2/2 (100%)
Pes planus	Yes	Yes	2/3	ND	ND	5/6	ND	ND	ND	ND	1	ND	8/10 (80%)
Ophthalmoplegia	Yes	Yes	3/3	ND	ND	1/6	3/9	3/5	1	2/2	ND	ND	13/26 (50%)
Nystagumus	No	No	2/3	2/2	ND	3/6	ND	1/3	ND	1/2	ND	ND	9/16 (56%)
optic atrophy	No	Yes	3/3	0/2	0/3	3/6	5/7	2/3	1	2/2	ND	ND	16/27 (59%)
Ptosis	Yes	Yes	2/3	ND	ND	ND	3/9	ND	1	1/2	ND	ND	7/15 (47%)
Strabismus	No	No	1/3	ND	ND	1/6	ND	ND	ND	2/2	1	ND	5/12 (42%)
Microcephaly	No	No	1/3	ND	ND	2/6	0/9	3/3	ND	0/2	ND	ND	6/23 (26%)
Cerebellar atrophy	No	No	0/3	0/2	3/3	2/6	0/9	0/3	0	0/2	1	0	6/31 (19%)
Cerebral atrophy	No	No	1/3	0/2	0/3	1/6	2/9	0/3	0	1/2	0	0	5/31 (16%)
Thining corpus callosum	No	No	1/3	0/2	0/3	1/6	2/9	0/3	0	1/2	0	0	5/31 (16%)
Delayed myelination	Yes	No	0/3	0/2	0/3	0/6	1/9	0/3	0	2/2	0	0	3/31 (10%)
Hearing impairment	Yes	Yes	0/3	0/2	0/3	2/5	2/9	1/5	ND	0/2	ND	0	5/30 (17%)
Feeding difficulty	Yes	Yes	3/3	ND	3/3	3/6	8/9	3/3	ND	2/2	ND	ND	22/26 (85%)
Dental misalignment	Yes	Yes	3/3	ND	ND	ND	ND	ND	ND	ND	ND	ND	3/3
Long face	Yes	Yes	3/3	ND	ND	ND	ND	ND	ND	ND	ND	ND	3/3
Low set ears	No	No	2/3	ND	ND	ND	ND	ND	ND	ND	ND	ND	2/3
Micrognathia	No	No	2/3	ND	ND	ND	ND	ND	ND	ND	ND	ND	2/3
High arched palate	Yes	Yes	1/3	ND	ND	ND	ND	ND	ND	ND	ND	ND	1/3
ABR abnormality	Yes	Yes	ND	ND	ND	ND	1/1	ND	0	1/2	ND	ND	2/4
Muscle biopsy abnormality	Yes	not done	ND	ND	ND	ND	ND	0/2	ND	ND	ND	ND	0/2
NCV abnormality	not done	not done	ND	ND	ND	ND	0/7	0/2	ND	0/2	ND	0	0/12
EEG abnormality	No	Yes	ND	ND	ND	2/6	ND	ND	ND	ND	ND	0	2/7
SSEP abnormality	Yes	Yes	ND	2/2	ND	ND	ND	ND	ND	ND	ND	ND	2/2

*3 probands among 5 patients are listed. Other members had no clinical description.

CAMRQ4, Cerebellar ataxia, mental retardation, and disequilibrium syndrome 4; Pt 1 and Pt 2, Patient 1 and Patient 2 in the present study; ND, not described; ABR, auditory brain stem responces; NCV, nerve conduction velocity; EEG, electroencephalogram; SSEP, short latency somatosensory evoked potentials.

were first observed in the present patients, indicating the degenerative nature of this gene variant.

Ataxic symptoms and hypotonia in patients with CAMRQ4 are indistinguishable from other genetic causes of developmental encephalopathy during the early developmental period, whereas visual and hearing impairments associated with involuntary movements and severe developmental delay may indicate CAMRQ4. Because ATP8A2 is strongly expressed in the cerebellum, ataxic symptoms (astasia-abasia, ataxic gait, or quadrupedal locomotion), nystagmus, head titubation, and cerebellar atrophy are recognized as cardinal indicators of cerebellar dysfunction, as shown in Table 1. Neuroanatomical studies have shown that the cerebellar output reaches vast areas of the neocortex, which may be related to the developmental disabilities in these patients (Buckner et al. 2011; Guell et al. 2018). However, early flattening on ABR and ophthalmoplegia as well as feeding difficulty and poor head control may indicate progressive brain stem dysfunction, although neuroimaging did not reveal brain stem atrophy.

ATP8A variants were first identified in autosomal recessive spontaneous wabbler-lethal (*wl*) mutant mice (Zhu et al. 2012). Although no study has reported on the neuropathology of a patient with CAMRQ4, neuropathological studies of *wl* mice demonstrated distal axonal degeneration and chromatolysis in parts of the central and peripheral nervous systems, without cell death (Zhu et al. 2012), which may partly explain why cerebellar atrophy is not pervasively recognized in patients.

Regarding the various movement disorders seen in patients, recent studies identified reciprocal connections between the cerebellum and basal ganglia, suggesting that these two subcortical structures are densely interconnected (Bostan et al. 2010; Pelzer et al. 2013), which may explain the coexistence of ataxia and choreoathetotic/dystonic movements.

In conclusion, patients with CAMRQ4 have consistent early onset neuromotor disorders and intellectual disabilities, which include infantile hypotonia, severe developmental delay, feeding difficulty, ptosis, ophthalmoplegia, areflexia, choreoathetosis, dystonia, and auditory and visual dysfunction. Clinically, the symptoms did not progress in the early period of development, which may make this difficult to distinguish from dyskinetic cerebral palsy, particularly in solitary cases. However, visual and hearing impairments associated with involuntary movements and severe developmental delay may be a clue to suspect CAMRQ4. Proper genetic diagnosis and genetic counseling may benefit families and medical practitioners by making family planning, reducing useless medical examination and exploring effective rehabilitation strategies.

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Conflict of Interest

The authors declare no conflict of interest.

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