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LETTER TO THE EDITOR

Spastic Paraplegia 82 in Two Asian Indian Siblings With *PCYT2* Mutations

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Dear Editor,

Hereditary spastic paraplegias (HSPs) constitute a heterogeneous group of inherited neurodegenerative disorders characterized by progressive weakness and spasticity of the lower limbs. HSPs are often accompanied by additional neurological symptoms, including ataxia, sensory loss, and cognitive impairment. HSPs can be classified according to inheritance pattern, clinical characteristics, or genetic mutations. HSPs can be broadly divided into two subgroups on the basis of their clinical characteristics: a pure form, which is characterized by spastic paraparesis and bladder disturbances with a loss of vibration sense, and a complicated form, which has additional manifestations, including ataxia, seizures, extrapyramidal disturbances, peripheral neuropathy, intellectual disability, dementia, gastroesophageal reflux, Dupuytren's disease, and varicose veins.[1] More than 80 genetic subtypes of HSP have been identified. The chromosomal loci of the HSP genes are termed spastic paraplegia (SPG) loci and are numbered in order of their discovery (starting with SPG1).[2]

Autosomal recessive spastic paraplegia 82 (SPG82) is characterized by mutations in the *PCYT2* gene, which is located on chromosome 17q25.3 and encodes a key enzyme involved in phosphatidylethanolamine biosynthesis, which is essential for proper neuronal function.[3] SPG82 is characterized by global developmental delay, intellectual impairment, progressive lower limb spasticity, visual impairment, nystagmus, and seizures.[3,4] Brain imaging of SPG82 patients shows progressive cerebral and cerebellar atrophy with nonspecific white matter hyperintensities.[3] Due to the rarity of this condition, the phenotypic spectrum and natural progression are still being studied, with ten case reports available to date. Here, we report two Asian Indian siblings with SPG82, with a focus on clinical presentation and genetics, to contribute to the increasing understanding of this rare disorder.

A 14-year-old female, the first child of nonconsanguineous parents, presented with delayed motor development milestones, progressive symmetric spastic paraparesis, gait and limb ataxia, scanning speech, and generalized tonic-clonic seizures from the age of 3 years. She did not exhibit any sensory symptoms or bowel or bladder disturbances. Her family history was positive for similar complaints in her younger brother (patient 2). On examination, her Montreal Cognitive Assessment (MoCA) score was 29/30, and her Addenbrooke's Cognitive Evaluation-III (ACE-III) score was 87/100. The results of a detailed lobar assessment were also normal. Scanning speech, bilateral square wave jerks, hypometric saccades, and bilateral gaze-evoked horizontal nystagmus were observed. Fundus examination results were normal. Motor examination revealed grade 1 spasticity in the bilateral upper limbs (modified Ashworth scale), grade 3 spasticity in the bilateral lower limbs, symmetric proximal predominant paraparesis, bilateral ankle contractures, and brisk deep tendon reflexes (DTRs) with an extensor plantar response. Cerebellar examination revealed titubation, dysmetria, dysdiadochokinesia, and abnormal results of the heel-shin test bilaterally. The patient had a wide-based stance with toe walking and a scissoring gait (Supplementary Video 1 in the online-only Data Supplement).

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A 9-year-old male presented with toe walking from the age of 2 years, eventually requiring support to ambulate. He exhibited stiffness in both lower limbs, difficulty getting up from the seated position, and slurred speech from the age of 4 years. He also developed generalized onset seizures from the age of 3 years. The patient was born at term via normal delivery and had delayed motor milestones. Examination revealed cerebellar dysarthria, impaired limb coordination, gait ataxia, and predominantly lower limb spasticity. Brisk DTRs and an extensor plantar response were observed (Supplementary Video 2 in the online-only Data Supplement). Fundus examination results were normal. His MoCA score was 28/30, and his ACE-III score was 85/100. A detailed lobar assessment did not reveal any deficits.

On the basis of clinical details, a syndromic diagnosis of early-onset spastic ataxia was made. The differential diagnoses included autosomal recessive spastic ataxia of Charlevoix-Saguenay, cerebrotendinous xanthomatosis, autosomal recessive complicated HSP, leukodystrophy, spinocerebellar ataxia, and ataxia with vitamin E deficiency. Details of the evaluation are listed in Table 1. The brain magnetic resonance images of both patients were normal, without evidence of cerebellar or callosal atrophy. Whole-exome sequencing of the peripheral venous blood of patient 1 revealed a pathogenic homozygous nonsense variant (c.1075C>T, p.Arg359*) in the *PCYT2* gene. Sanger sequencing of patient 2 revealed the same homozygous variant. Parental segregation revealed heterozygous variants in both the mother and father. A diagnosis of SPG82 was made. The patients were started on antiseizure medications, baclofen, and rigorous physiotherapy.

SPG82 is an extremely rare, recently described complicated HSP caused by homozygous or compound heterozygous mutations in the *PCYT2* gene. The protein encoded by this gene plays a rate-limiting role in the cytidine 5'-diphosphate-ethanolamine pathway, which is required for phosphatidylethanolamine and lipid ether synthesis.

In 2019, Vaz et al.[3] first described five patients ranging in age from 3–20 years from four unrelated families with a new complex HSP phenotype. Neurological manifestations included delayed motor development milestones, progressive spastic paraparesis, impaired intellectual development, and childhood-onset seizures. Brain images were normal early in the disease course but later revealed cerebral and cerebellar atrophy with white matter hyperintensities. Homozygous and compound heterozygous mutations in the *PCYT2* gene were identified, with 4/5 patients harboring the p.Arg377Ter variant. Compared with controls, patient fibroblasts revealed excessive accumulation of phosphatidylcholine ether phospholipids, with reduced activity of the *PCYT2* enzyme, in functional studies.

Since this initial report in 2019, SPG82 has been reported infrequently with additional phenotypic features (Table 2). In 2021, Kaiyrzhanov et al.[4] reported a patient with failure to thrive, early-onset severe retinal dystrophy, bilateral cataracts, progressive sensorineural hearing loss, epilepsy, cerebellar ataxia, and hyperreflexia. Imaging revealed cerebellar atrophy and dorsal cord atrophy. In 2020, Vélez-Santamaría et al.[5] reported two patients with *PCYT2* mutations. One of these patients was a 59-year-old male born to consanguineous parents who had been symptomatic since the age of 12 years. A mild pure HSP phenotype with normal neuroimaging was observed in this patient. The second patient was a 7-year-old male with dysmorphic features, spastic quadriparesis, developmental delay, intellectual disability, epilepsy, cerebellar ataxia, congenital cataracts, congenital nystagmus and optic atrophy. Magnetic resonance imaging of the brain revealed periventricular T2/fluid attenuated inversion recovery signal hyperintensities consistent with delayed myelination. Additional patients were reported by De Winter et

Table 1. Investigations in the two cases

Parameter	Patient 1	Patient 2
Hemoglobin (13–17 g/dL)	9.1	10.8
MCV (80–100 fl)/MCH (27–33 pg/RBC)	66.50/18.10	73.30/22.00
Liver and renal function test	Normal	Normal
Total protein (6.4–8.3 g/dL)/albumin (4.0–4.9 g/dL)	7.8/4.5	8.0/4.8
Vitamin B12 (197–771 pg/mL)/folate levels (3.1–17.5 ng/mL)	502/6	319/7
HIV, HBsAg, Anti HCV, serum VDRL	Negative	Negative
HbA1c (4.8%–5.6%)	5.9	4.8
Fasting lipid profile/alpha fetoprotein/serum vitamin E level	Normal	Normal
Nerve conduction studies: motor NCS, sensory NCS, f wave latency, sympathetic skin response, visual evoked potentials	Normal	Motor NCS-decreased amplitude with prolonged distal latencies in bilateral peroneal nerves Sensory NCS and f wave latency-normal study
TSH (0.27–4.20 μIU/mL)	6.23	5.30

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RBC, red blood cell; HIV, human immunodeficiency virus; HBsAg, hepatitis B antigen; Anti-HCV, anti-hepatitis C virus; VDRL, venereal diseases research laboratory; HbA1c, glycated hemoglobin A1c; NCS, nerve conduction studies; TSH, thyroid stimulating hormone.

Table 2. Summary of SPG82 cases reported in the literature

Author, year of publication	Number of cases	Age at onset/gender	Age at presentation	Main clinical features	Clinical signs	Neuroimaging	Variant
Vaz et al, 2019[3]	5	Not known/ male	5.8 years	Developmental delay, intellectual disability, regression, tonic clonic seizures	Spasticity, Hyperreflexia, bilateral extensor plantar response	Normal initially, progressive atrophy, subtle symmetric hyper intensities in cerebral white matter, MRS with voxel in affected white matter shows no lactate peak	Compound heterozygous variants c.920C>T (p.His244Tyr) and c.730C>T (p.Pro307Leu)
		16 years/ male	20 years	Development normal, motor milestones delayed, mild intellectual disability, regression, tonic clonic seizures	Spasticity, hyperreflexia, bilateral extensor plantar response	Normal initially, progressive atrophy, subtle symmetric hyper intensities in cerebral white matte	c.1129C>T p.[Arg377Ter]
		Not known/ male	16.7 years	Developmental delay, severe intellectual disability, regression, focal seizures/tonic clonic seizures	Spasticity, hyperreflexia, bilateral extensor plantar response	Progressive atrophy, symmetric hyperintensities in the cerebral white matter, MRS with voxel in affected white matter shows lactate peak	c.1129C>T p.[Arg377Ter]
		5.5 years/ female	9.9 years	Development normal, motor milestones delayed, mild Intellectual disability, regression, tonic clonic seizures	Spasticity, hyperreflexia, bilateral extensor plantar response	Progressive atrophy, subtle symmetric hyperintensities in the cerebral white matter	c.1129C>T p.[Arg377Ter]
		2 years/ male	2.5 years	Mild intellectual disability, focal seizures	Spasticity, hyperreflexia, bilateral extensor plantar response	Not done	c.1129C>T p.[Arg377Ter]
Vélez-Santamaría at al, 2020[5]	2	12 years/ male	59 years	Frequent falls, difficulty in running and climbing	Spasticity, hyperreflexia with clonus, extensor plantar response, hypopallesthesia of ankles	Normal	c.957G>C p.[Lys319Asn]
		Birth/male	7 years	Developmental delay, intellectual disability, epileptic seizures, swaying towards either side	Congenital lateral gaze nystagmus, cataract, optic atrophy cerebellar ataxia, optic atrophy, spasticity, hyperreflexia, extensor plantar response, dysmorphic features	Abnormal increased T2/FLAIR signal within the bilateral periventricular white matter suggestive of delayed myelination	Compound heterozygous variants: c.907delG (p. [Val303Ter] and c.1129C>T (p. Arg377Ter)
Wei et al, 2021[7]	1	17 years/ male	27 years	Abnormal walking	Spasticity in bilateral lower limbs	Normal	c.1130G>A (p. Arg377Glu)
De Winter et al, 2021[6]	1	20 months/ male	45 years	Gait instability, appendicular ataxia, anosmia, visual and speech disturbances	Saccadic ocular pursuits, dysarthria, scoliosis, truncal and appendicular ataxia, hyperreflexia, extensor plantar, loss of vibration, mild loss of proprioception	Initially normal, later (29 years of age) cerebellar atrophy, discrete cerebral atrophy	c.736G>A (p.Gly246Arg) and c.524_527del (p.Asp175Valfs*109)
Kaiyrzhanov et al, 2021[4]	1	Birth/female	26 years	Failure to thrive, reduced vision, generalized tonic clonic seizures, progressive hearing loss, gait abnormality	Retinal dystrophy, nystagmus, bilateral cataract, epilepsy, hyperreflexia	Cerebellar atrophy, spinal cord atrophy at thoracic level	Compound heterozygous c.1112+1G4A and c.743T4A p.(Val230Glu)

Table 2. Summary of SPG82 cases reported in the literature (continued)

Author, year of publication	Number of cases	Age at onset/gender	Age at presentation	Main clinical features	Clinical signs	Neuroimaging	Variant
Leonardis et al, 2022[8]	2 siblings	14 months/male	41 years	Gait unsteadiness, spasticity, seizures, myopia, cognitive decline, psychosis	Nystagmus, intention tremor, dysarthria, neuropathy	Frontoparietal white matter changes, parietal and cerebellar atrophy	
		2 years/male	53 years	Gait instability, seizures, spasticity	Nystagmus, intention tremor, dysarthria, neuropathy	Not done	Homozygous missense c.88T>G (p.Cys30Gly)
Mahungu et al, 2023[9]	1	Childhood/female	Not mentioned	Unsteady gait, spasticity	Complex HSP, sensorimotor neuropathy, optic neuropathy leading to blindness, seizures	Not mentioned	Homozygous missense c.736G>A (p.Gly246Arg)
Present study	2	3 years/female	14 years	Delayed motor development milestones, spastic paraparesis, ataxia, scanning speech, generalized tonic-clonic seizures	Bilateral square wave jerks, hypometric saccades, spastic paraparesis, pan cerebellar ataxia	Normal	c.1075C>T (p.Arg359*)
		2 year/male	9 years	Delayed motor development milestones, toe-walking, stiffness in lower limbs, slurring of speech, generalized tonic-clonic seizures	Lower limb predominant spasticity, pan cerebellar ataxia	Normal	c.1075C>T (p.Arg359*)

SPG82, spastic paraplegia 82; MRS, magnetic resonance spectroscopy; FLAIR, fluid attenuated inversion recovery; HSP, hereditary spastic paraplegia.

al.,[6] Wei et al.,[7] and Leonardis et al.[8] expanded the *PCYT2* phenotype of complex HSP to include sensorimotor axonal peripheral neuropathy. Mahungu et al.[9] reported another patient with spastic ataxia and peripheral and severe optic neuropathy. These findings suggest that onset at a very young age is associated with severe disease manifestations. In contrast to the above patients, our patients had normal neuroimaging results despite a long disease duration; other than nystagmus, these patients did not demonstrate any of the ophthalmological features, such as cataracts, optic atrophy, and retinal degeneration, previously reported in these disorders, particularly in patients with a younger age of onset. Our patients also exhibited preservation of cognitive skills.

Here, we report the first Asian Indian family with SPG82 presenting with a symptom complex of seizures, pancerebellar ataxia, and spastic paraparesis, adding to the limited literature on this rare complex HSP subtype.

Ethics Statement

The authors obtained written consent from the patient.

Supplementary Video Legends

Video 1. Video of patient 1 showing slow and hypometric saccades, spasticity with weakness of both lower limbs, brisk deep tendon reflexes, ankle clonus, dysmetria, and spastic-ataxic gait.

Video 2. Video of patient 2 showing cerebellar dysarthria, slow and hypometric saccades, spasticity with weakness of both lower limbs, brisk deep tendon reflexes, ankle clonus, and dysmetria.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.24259.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Anil Dash, Farsana Mustafa, Divyani Garg. Data curation: Anil Dash, Farsana Mustafa, Sreeja Samineni. Formal analysis: Anil Dash, Divyani Garg. Funding acquisition: Divyani Garg. Investigation: Anil Dash, Ajay Garg. Methodology: Divyani Garg. Project administration: Divyani Garg. Resources: Divyani Garg, Ayush Agarwal, Ajay Garg, Achal Kumar Srivastava. Software: Anil Dash, Ajay Garg. Supervision: Divyani Garg. Validation: Divyani Garg. Visualization: Divyani Garg. Writing—original draft: Anil Dash. Writing—review & editing: Farsana Mustafa, Divyani Garg, Sreeja Samineni, Ayush Agarwal, Ajay Garg, Achal Kumar Srivastava.

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