Rubina Dad, MPhil
Susan Walker, PhD
Stephen W. Scherer, PhD
Muhammad Jawad
Hassan, PhD
Mohammad Domaia
Alghamdi, MD
Berge A. Minassian, MD
Reem A. Alkhater, MD,
FRCP (C), MSc

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FEBRILE ATAXIA AND MYOKYMIA BROADEN THE SPG26 HEREDITARY SPASTIC PARAPLEGIA PHENOTYPE

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Hereditary spastic paraplegias (SPGs) are among the genetically most diverse neurologic disorders with over 70 loci identified.^{1,2} The recessively inherited SPG26 is caused by mutations in *B4GALNT1*, encoding the β -1-4-N-acetyl-galactosaminyl transferase which functions in the biosynthesis of complex glycosphingolipids. To date, 12 families have been reported in 3 publications, with a broad phenotypic spectrum within and between families (table 1). We add a new family to the literature with 3 affected members and a remarkable phenotype of purely fever-induced ataxia with myokymia. We also review all published cases^{3–5} to encapsulate the current knowledge of the neurologic features and spectrum of this disease.

Our proband presented at age 5 years with severe fever-induced ataxia and myokymia, the latter in the flexor muscles of the hands and feet, which additionally exhibited carpopedal spasm. Presumed postviral cerebellitis, he was treated with methylprednisolone and IV immunoglobulin and recovered fully in a week. He had 4 additional identical episodes until age 10, all induced by a febrile illness (39–40°C), each self-resolving, untreated, following defervescence. Examination at age 11 shows proximal muscle weakness, mild lower limb spasticity, preserved deep tendon reflexes and sensation, intact cognition, normal brain MRI, and evidence of peripheral neuropathy on nerve conduction study. His parents are first-degree cousins, and he has 2 older sisters and 1 older brother. The sisters are lean and tall with relative microcephaly, and on examination have reduced muscle bulk, proximal muscle weakness, and mildly spastic gait. The elder sister had had Achilles tendon release surgery at age 8 but continued to have lower limb spasticity. Her and affected brother's Spastic Paraplegia Rating Scale scores were 4/52 and 13/52, respectively (tables e-1 and e-2 at Neurology.org/ng). The older brother was and remains healthy. Whole-exome sequencing (e-Methods) for proband and 1 sister revealed a single significant shared homozygous variant, namely *B4GALNT1* chr12:58021427:G>C;

NM_001478: c.C1358G; p.Pro453Arg. No other known SPG, myokymia, or ataxia-related genes harbored clinically relevant variants (table e-3). Sanger sequencing in all family members confirmed that the *B4GALNT1* change was homozygous in proband and sisters and heterozygous in healthy brother and parents. It was not present in the 1000 Genomes European, American, Asian, or African databases, dbSNP or ExAC. The variant was predicted damaging by PolyPhen2 and CADD and evolutionarily conserved (PhyloP). No further functional consequences could be predicted.

A summary of all SPG26 published cases (table 1) reveals spastic paraparesis as a commonly shared core symptom. The disease extends to other systems and includes dysarthria, ataxia, intellectual disability, and psychiatric manifestations, none of which is uniformly present across families and even within families. Onset is in childhood, usually before age 10, in all families except 1, with a missense mutation and onset between 28 and 39 years. In this family, despite late onset, progression was rapid, with severe muscle wasting.³ Our family, with another missense mutation, appears to be the mildest to date among childhood-onset cases, and the phenotype is particularly mild in the 2 girls (table 1). They had a later age at onset than the boy (8 vs 5), and, despite being older (15 and 21 vs 11), have no muscle wasting or ataxia and only mild spasticity. Finally, the male patient manifests a symptom set not previously reported, namely febrile ataxia and myokymia with full recovery after each attack.

Complex glycosphingolipids (e.g., GM1 or GD1a gangliosides) are crucial components of plasma membranes but are by far most abundant in nervous tissue. Their 2 principal roles are to mediate cell-cell interactions and regulate membrane protein functions. Additional functions include endocytosis, signal transduction, and synaptic plasticity. Complex glycosphingolipids represent a family of many molecules, the shared “glyco” component consisting of 4 glucans serially added to the sphingolipid during biosynthesis. *B4GALNT1* catalyzes the addition of the third (N-acetyl- β -D-galactosamine) to the second glucan, and the absence of the enzyme results in non-progression to the more complex forms (e.g., from GM3 to GM2 and GM1).⁶ *B4galnt1* knockout mice

Supplemental data at
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Table 1 Summary of clinical features of all published cases with *B4GALNT1* mutations (NM_001478)

	Present study		Reference 5		Reference 4						Reference 3			
Families	Saudi		Bedouin	Bedouin	Spanish	Tunisian	Brazilian	Algerian	Portuguese	French	German	Kuwaiti	Italian	Amish
Affected	2 girls	1 boy	4	5	3	4	5	1	4	1	3	5	2	4
Age at onset, y	8	5	Early childhood	6-7	7-8	3-19	9-14	11	2-3	Early	Early	6-11	28-39	Second year of life
Dysarthria	No	Mild	Severe	Severe	NS	1 yes, 3 no	No	No	Mild	Mod	No-sev	No-sev	NS	NS
Spasticity	Mild	Mod	Severe	Severe	Yes, NOS	Mod-sev	Mod-sev	Mod	Mild-mod	Severe	Mod-sev	Mod	Mod-sev	Mod
Ataxia	No	Febrile	Severe	Severe	Yes	No	Mild	Moderate	Mild-mod	Severe	No	Severe	Mod-sev	Mod-sev
Reflexes	Normal	Normal	↓	↓	Brisk	Brisk	Brisk	Brisk	↓	NS	Normal	↓	↓	↓
Muscle wasting	No	No	Severe	Severe	Moderate	No-sev	No	No	Mild-sev	Severe	Mod-sev	Severe	Severe	Mild-mod
Other					Cataract	Dysmorphism								Seizure
Behavior and cognition	Normal	Normal	Autism, mod-sev ID	Emotional lability, mild ID	Mild-mod ID	Mild-mod ID	Mild-mod ID	Mild-mod ID	Mild-mod ID	Mild-mod ID	Mild-mod ID	Emotional lability, severe ID	Mild-severe ID	Autism, mild-mod ID
Brain or spinal MRI	Normal	Normal	Normal	Normal	Cerebral atrophy	Normal in 1, ND in 3	Normal	Cerebral atrophy	Subcortical periventricular WMH	Cerebral atrophy	Normal (CT)	Normal	Congenital spinal stenosis	ND
NCS/EMG	Normal	Axonal neuropathy	ND	ND	Axonal neuropathy; pes cavus	Normal in 1, ND in 3	Normal	Axonal neuropathy	Pes cavus and clinical peripheral neuropathy	Axonal neuropathy	Axonal neuropathy	Normal	Decreased sensory amplitudes	Pes cavus and clinical peripheral neuropathy
Mutations	c.C1358G; p.Pro453Arg		c.1003-2A>G	c.1458_1459 insA; p. Leu487*fs	c.395delC; p. Pro132Glnfs*7	c.898C>T; p.Arg300Cys	c.682C>T; p. Arg228*	c.263 dupG; p.Leu89fs*13	c.358C>T; p.Gln120*	c.917_922dup; p.Thr307_Val308dup; c.1315_1317delTTC; p.Phe439del	c.1298A>C; p.Asp433Ala	c.1458 dup; p. Leu487Thrfs*77	c.852 G>C; p. Lys284Asn	c.1514 G>A; p. Arg505His

Abbreviations: ID = intellectual disability; Mod = moderate; NCS = nerve conduction study; ND = not determined; NOS = not otherwise specified; NS = not specified; Sev = severe; WMH = white matter hyperintensity.

The downward arrow indicates decreased deep tendon reflex.

are healthy, suggesting that shorter gangliosides (e.g., GM3) largely compensate for absent longer forms.⁷ This appears to be the case also in humans, as evidenced by the patients discussed here, but only for the years until disease onset. After that, there is progressive neurologic decompensation. Precisely, which complex ganglioside deficiency(ies) in which cell types, regions or pathways underlie the upper and lower motor neuron disease and other aspects of SPG26 await future studies. This knowledge will help elucidate the roles of complex glycosphingolipids in the development and function of the central and peripheral nervous systems.

From the Atta-ur Rahman School of Applied Biosciences (R.D., M.J.H.), National University of Sciences and Technology (NUST), Pakistan; Program in Genetics and Genome Biology (R.D., B.A.M.), Division of Neurology (B.A.M.), Department of Paediatrics, and The Centre for Applied Genomics, Genetics and Genome Biology (S.W., S.W.S.), The Hospital for Sick Children; Department of Molecular Genetics (S.W.S.), and McLaughlin Centre (S.W.S.), University of Toronto, Ontario, Canada; and Department of Pediatrics (M.D.A., R.A.A.), Division of Neurology, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia.

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Correspondence to Dr. Alkhatir: Reem.khatir@jhah.com

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Febrile ataxia and myokymia broaden the SPG26 hereditary spastic paraplegia phenotype

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