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Altered CSF levels of monoamines in hereditary spastic paraparesis 10

A case series

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Abstract

Objective

To perform a comprehensive clinical characterization and biochemical CSF profile analyses in 2 Swedish families with hereditary spastic paraparesis (HSP) 10 (SPG10) caused by 2 different mutations in the neuronal kinesin heavy chain gene (*KIF5A*).

Methods

Structured clinical assessment, genetic studies, and neuroradiologic and electrophysiological evaluations were performed in 4 patients from 2 families with SPG10. Additional CSF analysis was conducted in 3 patients with regard to levels of neurodegenerative markers and monoamine metabolism.

Results

All patients exhibited a complex form of HSP with a mild to moderate concurrent axonal polyneuropathy. The heterozygous missense mutations c.767A>G and c.967C>T in *KIF5A* were found. Wide intrafamilial phenotype variability was evident in both families. CSF analysis demonstrated a mild elevation of neurofilament light (NFL) chain in the patient with longest disease duration. Unexpectedly, all patients exhibited increased levels of the dopamine metabolite, homovanillic acid, whereas decreased levels of the noradrenergic metabolite, 3-methoxy-4-hydroxyphenylglycol, were found in 2 of 3 patients.

Conclusions

We report on CSF abnormalities in SPG10, demonstrating that NFL elevation is not a mandatory finding but may appear after long-standing disease. Impaired transportation of synaptic proteins may be a possible explanation for the increased dopaminergic turnover and noradrenergic deficiency identified. The reasons for these selective abnormalities, unrelated to obvious clinical features, remain to be explained. Our findings need further confirmation in larger cohorts of patients harboring *KIF5A* mutations.

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Glossary

5-HIAA = 5-hydroxyindoleacetic acid; **ALS** = amyotrophic lateral sclerosis; **HSP** = hereditary spastic paraparesis; **HVA** = homovanillic acid; ***KIF5A*** = neuronal kinesin heavy chain gene; **MHPG** = 3-methoxy-4-hydroxyphenylglycol; **NFL** = neurofilament light; **PNP** = polyneuropathy; **SPRS** = Spastic Paraplegia Rating Scale.

Hereditary spastic paraparesis (HSP) comprises a large and growing group of chronic progressive neurodegenerative diseases with varying patterns of inheritance, age at onset, and disease severity. These diseases share a common affection of the corticospinal tracts. Heterozygous mutations in the N-terminal motor domain of the neuronal kinesin heavy chain gene (*KIF5A*) are associated with autosomal dominant HSP 10 (SPG10) and less commonly with Charcot-Marie-Tooth type 2, with or without pyramidal signs.[1,2] Rarely, mutations in this gene are also associated with cerebellar ataxia or cognitive impairment.[2] In addition, a recent genome-wide association study has identified variants in the C-terminal of *KIF5A* associated with amyotrophic lateral sclerosis (ALS).[3]

KIF5A encodes one of 2 heavy chain subunits that together with 2 light chain subunits make up a tetrameric kinesin-1 protein.[1,4,5] This kinesin is crucial for anterograde molecular axonal transport by binding to microtubule.[4,6] At least 23 mutations in *KIF5A* with HSP phenotype have been reported.[1,2,5,7,8]

In vitro assays have demonstrated that mutant forms of the kinesin-1 protein impair the transport of cargo along microtubule.[6] Furthermore, 2 studies on cultured neurons from *Kif5A* knockout mice and mice with mutant *Kif5A* have demonstrated disturbed axonal bidirectional transport of mitochondria and neurofilaments, respectively.[9,10] Thus, in patients, *KIF5A* mutations are believed responsible for an axonopathy damaging both the central and peripheral nervous systems.[1,5,7] Here, we hypothesized that patients with SPG10 would demonstrate an elevation of neurofilament light (NFL) chain in CSF.

Methods

Standard protocol approvals, registrations, and patient consents

All patients have given oral and written consent to this characterization approved by the regional ethical board in Stockholm, Sweden (2016/2503-31/2).

Clinical assessments

Patients with a known diagnosis of SPG10, followed at Karolinska University Hospital, were eligible for the study. In total, 4 patients from 2 Swedish families (A and B) with heterozygous *KIF5A* mutations were included (figure). Patients were assessed with standardized clinical examination that included the Spastic Paraplegia Rating Scale (SPRS), Friedreich Ataxia Rating Scale part 1: functional staging for ataxia, Inventory of Non-Ataxia Signs, Instituto de Pesquisa Clinica Evandro Chagas Scale, Scale for the Assessment and Rating of Ataxia, and Montreal Cognitive Assessment. The inclusion of rating scales assessing cerebellar function was chosen based on reports of ataxia as a feature in patients with *KIF5A* mutations and other familial kinesin motor proteinopathies.[2,11] Standardized examination took place between January and March of 2018.

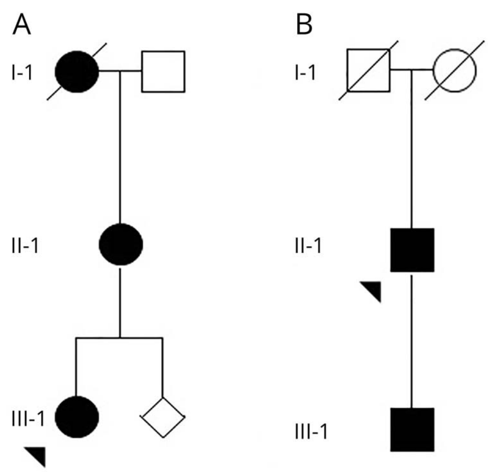
Genetic analyses

Both families were examined with targeted genetic analyses for autosomal dominant HSP (e-Methods, links.lww.com/NXG/A160).

Biochemical analyses

CSF was collected from 3 patients (III:1 in family A and II:1, III:1 in family B) by standard procedures. Patient II:1, in family A, declined lumbar puncture. For patient III:1, in family A, CSF had been collected in 2012 and since then stored at −80°C. Levels of the neurodegenerative markers total tau (t-tau), phosphorylated tau (p-tau), β-amyloid 42/40 (Aβ42/40) ratio, and NFL chain and monoamine metabolites homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined (e-Methods, links.lww.com/NXG/A160).

Figure Pedigrees of the 2 Swedish families with SPG10



Pedigrees of family A and B harboring the c.767A>G (p.Asn256Ser) and c.967C>T (p.Arg323Trp) mutations in *KIF5A*, respectively. Patient I:1 in family A, due to lack of comprehensive medical notes, is considered possibly symptomatic based on historical description.

Electrophysiology

Motor and sensory nerve conduction studies were compiled from all 4 patients including, at a minimum, unilateral assessment of the median, peroneal, tibial, and sural nerves. Nerve conduction studies were conducted with Natus, Viking EDX (Cephalon A/S; Denmark). Quantitative sensory testing, detecting perception thresholds for cold and heat, was assessed bilaterally in the lateral foot and unilaterally in the hand with Medusa, TSA II (Cephalon A/S; Denmark).

Neuroimaging

Historic data from brain and spinal cord MRI were compiled and reviewed.

Data availability statement

Anonymized data will be shared by request from any qualified investigator.

Results

The previously reported heterozygous mutations in *KIF5A*, c.767A>G (p.Asn256Ser) and c.967C>T (p.Arg323Trp) were found in family A and B, respectively.[1,5] Briefly, all the affected patients presented with a variable degree of spastic paraparesis, which is in line with previous descriptions.[1,2,5,7,8] Onset was at adult age in all but one case (III:1 in family B), in which the onset was insidious during childhood. All patients had variable degrees of polyneuropathy (PNP). The index case in family B reported neuropathic symptoms many years after onset of paraparesis, and electrodiagnostic testing demonstrated a moderate axonal sensorimotor PNP. The historical rate of overall clinical progression was slow in both families. We did not find evidence of cerebellar ataxia, psychiatric symptoms, or cognitive impairment. None of the patients were treated with psychotropic medications. Neuroimaging was normal. A summary of clinical, radiologic, and electrodiagnostic characteristics for both families is shown in table 1.

CSF-NFL was elevated only in the patient with the longest disease duration. In addition, and more unexpected, we found in all tested patients elevated CSF-HVA levels, and in 2 patients, CSF-MHPG was reduced. The serotonin metabolite (5-HIAA), Aβ42/40 ratio, and t-tau and p-tau levels were normal. Results from CSF analyses are presented in table 2. Detailed case descriptions are included in the supplemental data (e-Clinical phenotypes, links.lww.com/NXG/A161).

Discussion

There is a need for biomarkers and disease-modifying treatments for HSP diseases. The reasons for intrafamilial phenotype variability in SPG10 remain to be elucidated.[1,7] This variation is similar to what is seen in other forms of familial

Table 1 Electrodiagnostic, neuroradiologic, genetic, and clinical features of 2 families with SPG10

Patient	Age at onset (y)	Presenting symptoms	Age at study inclusion (y)	Genotype	MoCA	SPRS	Pyramidal signs	FARS stage	INAS count	IPEC	SARA	Brain MRI	Spine MRI	NCS and QST
A I:1	50–60[a]	Impaired gait	Died at age 90	—	—	—	—	—	—	—	—	—	—	—
A II:1	33	Impaired gait	67	c.767A>G	28	11	Hyperreflexia, spastic gait, and Babinski sign	2	5	7	4	—	NAD	Mild mixed sensorimotor PNP including small fibers (C and Aδ)
A III:1	34	Impaired gait and leg cramps	45	c.767A>G	28	19	Hyperreflexia, ankle clonus, spastic gait, and Babinski sign	3.5	6	14	6	NAD	NAD	Mild axonal sensory PNP
B II:1	26	Impaired gait and imbalance	66	c.967C>T	26	26	Pronounced scissor gait and equivocal Babinski sign	4	4	12	12.5	NAD	NAD	Moderate axonal sensorimotor PNP
B III:1	Childhood	Impaired gait and paresthesia	32	c.967C>T	30	7	Spastic gait, ankle clonus, and equivocal Babinski sign	2	6	4	3	NAD	NAD	Moderate axonal sensorimotor PNP including small fibers (Aδ)

Abbreviations: FARS stage = Friedreich Ataxia Rating Scale part 1, Functional Staging for Ataxia; INAS count = Inventory of Non-Ataxia Signs; IPEC = Instituto de Pesquisa Clinica Evandro Chagas Scale; mixed = axonal and demyelinating features present; MoCA = Montreal Cognitive Assessment; NAD = nothing abnormal detected; NCS = nerve conduction study; PNP = polyneuropathy; QST = quantitative sensory testing; SARA = Scale for the Assessment and Rating of Ataxia; SPRS = Spastic Paraplegia Rating Scale.
Results from ancillary testing and clinical examination. All clinical rating scales have been conducted in the spring of 2018.
[a] Clinical data based on the historical account provided by the patient's daughter (e-Clinical phenotypes, links.lww.com/NXG/A161).

Table 2 CSF profiles of 3 patients with SPG10

Patient	t-Tau (pg/mL) [<300 (18–45 years)] [<400 (>45 years)]	p-Tau (pg/mL) [<60 (20–60 years)] [<80 (>60 years)]	Aβ42/40 [>0.89]	NFL (pg/mL) [<560 (30–39 years)] [<1850 (>60 years)]	HVA (nmol/L) [40–170]	5-HIAA (nmol/L) [50–170]	MHPG (nmol/L) [65–140]
A I:1	—	—	—	—	—	—	—
A II:1	—	—	—	—	—	—	—
A III:1	24	26	0.90	517	208[a]	141	38[a]
B II:1	320	45	1.07	2,285[a]	237[a]	107	87
B III:1	171	32	1.02	432	272[a]	101	60[a]

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; NFL = neurofilament light.
Biochemical characteristics of 3 patients with regard to markers of neurodegeneration and monoamine metabolism. A significant elevation of NFL in the patient in family B with the longest disease duration (II:1) is demonstrated, possibly reflecting axonal damage. Elevated HVA, reflecting increased dopamine turnover, is seen in all 3 patients. Furthermore, in 2 patients, biochemical signs of decreased noradrenergic turnover are present.
[a] Indicates value outside reference range.

kinesin motor proteinopathies such as SPG30 (*KIF1A*) and SPG58 (*KIF1C*); however, these diseases are biallelic and present with a more severe phenotype than SPG10.[11,12]

An impairment of axonal transport, with resulting length-dependent axonal degeneration, forms the main theory of the underlying pathophysiology in SPG10.[1] CSF levels of NFL, an important cytoskeletal component of the axon, were mildly elevated in the patient with longest disease duration. This patient also demonstrated the highest SPRS score (table 1). Because mutated *KIF5A* is known to impair axonal transport of neurofilaments, at least in vitro, we were expecting a more general elevation in our patients.[9] However, NFL elevation was not evident in the 2 younger patients why such elevation cannot be viewed as an obligate finding in SPG10. These results are in contrast with studies in ALS, where NFL has been proposed as a biomarker.[13] Furthermore, elevated CSF levels of phosphorylated neurofilament heavy chain in patients with HSP (n = 9) compared with controls have been reported in a previous study.[14] It will be interesting to study NFL levels in patients with ALS harboring *KIF5A* mutations.

Assuming that intact axonal transport is important to maintain synaptic supply of monoamines, we analyzed these metabolites. Surprisingly, CSF-HVA was elevated in all tested patients, of which none had a history of mood disturbance, psychotic behaviors, or treatment with psychotropic drugs. Thus, the clinical correlates of this abnormality is unclear. In addition, 2 patients had decreased levels of the noradrenergic metabolite MHPG in CSF. In keeping with the proposed pathophysiology of an underlying axonopathy in SPG10, deficiency of various neurotransmitters such as noradrenaline may either reflect impaired transportation of synaptic proteins or an epiphenomenon. Regardless, the specificity of these abnormalities remains to be explained.

Small sample size is the main limitation of this study. In addition, we cannot rule out that the prolonged CSF storage time (III:1 in family A) might have underestimated the values of t-tau and Aβ42/40 ratio.

Previous reports on the CSF profile in patients with *KIF5A* mutations are rare. Thus, future studies in larger cohorts are needed to better discern whether noradrenergic deficiency and increased dopaminergic neurotransmission are prevalent findings in SPG10, other kinesin proteinopathies, and/or patients with ALS with *KIF5A* mutations. It will also be important to delineate potential clinical correlates to these changes in monoaminergic neurotransmission.

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Disclosure
M. Andréasson has received a contribution from NEURO Sweden (Neuroförbundet) for another study. K. Lagerstedt-Robinson and K. Samuelsson report no disclosures. G. Solders has received an unconditional grant from Sanofi/Genzyme for another study. K. Blennow has served as a consultant or at advisory boards for Alector, Alzheon, CogRx, Biogen, Lilly, Novartis, and Roche Diagnostics and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg, all unrelated to the work presented in this article. M. Paucar and P. Svenningsson report no disclosures. Go to Neurology.org/NG for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
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Kristina Lagerstedt-Robinson, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm	Author	Interpretation of genetic tests and revision of the manuscript
Kristin Samuelsson, MD, PhD	Karolinska University Hospital, Stockholm	Author	Interpretation of data and revision of the manuscript
Göran Solders, MD, PhD	Karolinska University Hospital, Stockholm	Author	Interpretation of neurophysiologic studies and clinical data and revision of the manuscript
Kaj Blennow, MD, PhD	Clinical Neuroscience, University of Gothenburg	Author	CSF analyses; interpretation of data; and revision of the manuscript
Martin Paucar, MD, PhD	Karolinska University Hospital and Karolinska Institute, Stockholm	Author	Revision of the manuscript; study concept and design; analysis and interpretation of data; and study supervision and coordination
Per Svenningsson, MD, PhD	Karolinska University Hospital and Karolinska Institute, Stockholm	Author	Revision of the manuscript; analysis and interpretation of data; study supervision and coordination; and obtaining funding

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