

The neurological and ophthalmological manifestations of *SPG4*-related hereditary spastic paraplegia

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Received: 23 October 2012 / Accepted: 29 November 2012 / Published online: 13 December 2012
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Dear Sirs,

The hereditary spastic paraplegias (HSPs) are a genetically heterogeneous group of disorders characterised by progressive corticospinal tract degeneration and the development of lower limb spasticity [1, 2]. Autosomal-dominant HSP is the most commonly inherited form of the disease and in this group, *SPG4* mutations account for ~40 % of cases [1]. The *SPG4* gene codes for spastin, a critical neuronal protein that maintains organelle axonal transport by severing and rearranging the microtubule network [3, 4]. Dysfunctional mutant proteins or insufficient quantities of the wild-type protein inhibit this dynamic shuttling process resulting

in axonal swelling and progressive retrograde degeneration that preferentially affects the long corticospinal axons [3, 4].

There is mounting evidence that the microtubule and mitochondrial networks are intrinsically linked at the cellular level [5]. This intriguing association has recently been highlighted by the clinical observation that autosomal-dominant optic atrophy (DOA)—a classical mitochondrial optic neuropathy caused by pathogenic *OPA1* mutations—can result in complicated neurological phenotypes (DOA+) with features indistinguishable from HSP [6]. Furthermore, subclinical corticospinal tract dysfunction also seems to be a prevalent feature among *OPA1* mutation carriers presenting with isolated visual failure, suggesting a wider disease spectrum than originally considered [7]. Interestingly, these overlapping genotype-phenotype manifestations have been reported previously in families with a rarer, autosomal-recessive form of HSP caused by pathogenic *SPG7* mutations, in which bilateral optic atrophy was a prominent feature segregating with spastic paraplegia [8–10]. Given the emerging disease mechanisms linking corticospinal tract dysfunction with optic nerve degeneration, the aim of this study was to determine the neurological and ophthalmological manifestations of *SPG4*-related HSP, looking specifically for evidence of clinical or subclinical optic neuropathy among affected patients. The overall neurological disability, including cognitive function, was also evaluated to provide a comprehensive assessment of the burden of disease in this group of patients.

A comprehensive neurological (GP, RH, PFC) and ophthalmological (PYWM) assessment (Supplementary Method) was carried out on ten white patients from the North of England harbouring confirmed pathogenic *SPG4* mutations (Table 1). A broad spectrum of

Electronic supplementary material The online version of this article (doi:[10.1007/s00415-012-6780-3](https://doi.org/10.1007/s00415-012-6780-3)) contains supplementary material, which is available to authorized users.

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Table 1 Molecular genetic and ophthalmological features of the *SPG4* patient cohort

Patient	Sex	Age (years)	SPG4 mutation		BCVA RE-LE	Optic discs/OCT measurements	Eye movements	Visual electrophysiology
			Exon	cDNA change/consequence				
1	F	31	5	c.743C>G/p.S245X	20/20-20/20	Normal/no RNFL thinning	Normal	Normal
2	M	53	5	c.743C>G/p.S245X	20/20-20/20	Normal/no RNFL thinning	Horizontal SWJ/saccadic pursuit	Normal
3	F	50	6	c.937delG/p.D313fsX1	20/20-20/20	Normal/no RNFL thinning	Normal	Normal
4	F	55	4–17	del exon 4-17/large-scale deletion	20/20-20/20	Normal/no RNFL thinning	Normal	Normal
5	F	29	10	c.1253_1255delAAG/p.E418fsX198	20/20-20/20	Normal/no RNFL thinning	Horizontal SWJ/saccadic pursuit	Normal
6	F	25	11	c.1442_1443insA/p.V482fsX5	20/20-20/20	Normal/no RNFL thinning	Normal	Normal
7	F	55	11	c.1442_1443insA/p.V482fsX5	20/20-20/20	Normal/no RNFL thinning	Horizontal SWJ/saccadic pursuit	Normal
8	F	49	11	c.1414G>A/p.V472I	20/20-20/20	Normal/no RNFL thinning	Normal	Normal
9	F	72	11	c.1384A>G/p.K462E	20/60-20/30	Normal/no RNFL thinning	Normal	Normal
10	M	65	11	c.1081C>A; c.1082T>A/p.L361N	20/20-20/20	Normal/no RNFL thinning	Normal	Normal

BCVA best-corrected visual acuities, cDNA complementary DNA, LE left eye, OCT optical coherence tomography, RE right eye, RNFL retinal nerve fibre layer, SWJ square wave jerks

neurological disability was observed among affected patients with scores ranging from one to nine on the modified EDSS scale (Table 2). Importantly, four patients had abnormal MOCA scores of less than 26 points. Seven patients performed poorly on the memory component of the MOCA test protocol and one patient had abnormal visuospatial/executive performance. The association between *SPG4* mutations and progressive cognitive decline remains controversial [11–13] and our study of a well-characterised patient cohort provides further evidence favouring a true causal link. Two of the patients with abnormal MOCA scores were younger than the age of 30 years, clearly highlighting the need for clinical vigilance to detect early signs of cognitive impairment and to provide adequate level of support, especially to carers.

Except for one patient who had bilateral nuclear sclerotic cataracts, all patients had best-corrected visual

acuities of 20/20 bilaterally (Table 1). The ophthalmological examination was normal with full colour discrimination and no detectable optic disc or retinal abnormalities. Visual fields, RNFL thickness measurements and visual electrophysiology were within the normal range for the entire HSP patient cohort. Three patients had abnormal eye movements with horizontal square wave jerks and saccadic smooth pursuits. No significant ptosis or limitation of eye movements was noted on orthoptic assessment. Based on our comprehensive clinical and electrophysiological evaluation, visual loss secondary to optic nerve or retinal degeneration is unlikely to be a major phenotypic manifestation of *SPG4*-related disease. Affected patients and at-risk family members can therefore be reassured that unlike other genetically-determined forms of HSP [6–10], *SPG4* mutations are not associated with the development of significant ophthalmological complications, in particular visual failure.

Table 2 Neurological and cognitive features of the SPG4 patient cohort

Patient	Cognitive assessment (MOCA)	Motor examination												Vibration sense	Other findings	Disability measurements			
		Modified Ashworth spasticity score						Deep tendon reflexes									Power (MRC scale)	Coordination	
		L/R E	L/R K	L/R BR	L/R B	L/R T	L/R P	L/R A	L/R PR	UL ex/ft	LL fl/ex								
Score	Comments	L/R	L/R	L/R	L/R	L/R	L/R	L/R	PR	UL	LL	10 m walk	Modified EDSS						
1	27/30	3 points from memory	0, 0	3, 3	3, 3	3, 3	3, 3	4, 4	2, 2	2, 2	2, 2	Ex	5, 5	4, 5	AT	Ankles	19.1 s	6.5	
2	27/30	4 points from memory	0, 0	1, 1	2, 2	2, 2	2, 2	3, 3	2, 2	3, 3	2, 2	Fl	5, 5	5, 5	N	N	8.2 s	1	
3	27/30	2 points each from visuospatial/ executive and attention	0, 0	1, 1	2, 2	2, 2	2, 2	3, 3	2, 2	3, 3	2, 2	Ex	5, 5	4, 4	N	Knees	10.1 s	2	
4	27/30	3 points from memory	0, 0	2, 2	3, 3	3, 3	2, 2	3, 3	2, 2	3, 3	2, 2	Ex	5, 5	4, 3–4	N	Knees	Marked LL oedema	WC	7
5	23/30	3 points from memory	3, 3	4, 4	3, 3	3, 3	3, 3	3, 3	3, 3	4, 4	4, 4	Ex	4, 4	0, 0	N	Knees	Spastic dysarthria	WC	9
6	25/30	3 points from memory	0, 0	1, 1	2, 2	2, 2	2, 2	3, 3	3, 3	3, 3	3, 3	Fl	5, 5	5, 5	N	N	8.9 s	1	
7	25/30	5 points from memory	0, 0	3, 3	2, 2	3, 3	3, 3	4, 4	3, 3	4, 4	3, 3	Ex	5, 5	4, 5	N	Ankles	13.4 s	4	
8	29/30		0, 0	3, 3	2, 2	2, 2	2, 2	4, 4	4, 4	4, 4	4, 4	Ex	5, 5	4, 4	N	N	11.3 s	2	
10	25/30	4 points from memory	1, 1	2, 2	2, 2	2, 2	2, 2	3, 3	3, 3	3, 3	3, 3	Ex	5, 5	4, 4	N	Ankles	Two canes needed for walking	36.6 s	6.5

Patient nine was not available for this portion of the assessment. A total MOCA score of 26 or higher is considered normal. For subjects with 12 years of total education or less, an additional point is added. MOCA scores lower than 26 are suggestive of cognitive impairment [14]. Vibration sense has been reported as the lowest normal testing location. Published normative range for the 10 m walk test protocol: mean 6.7 s, 95 % confidence interval 5.6–7.9 s [15]

A Achilles, AT action tremor, B biceps, BR brachioradialis, E elbow, EDSS Expanded Disability Status Scale, Ex extensor, Fl flexor, K knee, L left, LL lower limbs, m metres, MOCA Montreal Cognitive Assessment Scale, MRC Medical Research Council, N normal, PR plantar responses, R right, s seconds, T triceps, UL upper limbs, WC wheelchair-bound

Acknowledgments This work was supported by a research grant from the Association of British Neurologists (ABN, UK). GP is the recipient of a Bisby Fellowship from the Canadian Institutes of Health Research. RH is supported by the Medical Research Council (MRC, UK). PFC is a Wellcome Trust Senior Fellow in Clinical Science and a UK National Institute of Health Research (NIHR) Senior Investigator who also receives funding from the MRC (UK), and the UK NIHR Biomedical Research Centre for Ageing and Age-related disease award to the Newcastle upon Tyne Hospitals NHS Foundation Trust. PYWM is an MRC (UK) Clinician Scientist.

Conflicts of interest All the listed authors in this manuscript report no relevant financial disclosures or conflicts of interest.

Ethical standard This study had the relevant institutional ethical approval and it was carried out in compliance with the Declaration of Helsinki.

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