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ORIGINAL ARTICLE

Multiple sclerosis in patients with hereditary spastic paraplegia: a case report and systematic review

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Abstract

Introduction An increasing number of cases of comorbid hereditary spastic paraplegia (HSP) and multiple sclerosis (MS) have been described. We report a patient with the SPG3A form of HSP and features of relapsing-remitting MS (RRMS). We took this opportunity to review the current literature of co-occurring MS and HSP.

Method The patient underwent clinical, laboratory and neuroimaging evaluations. We performed a literature search for cases of HSP and MS. The 2017 McDonalds Criteria for MS were retrospectively applied to the selected cases.

Results A 34-year-old woman, presenting a molecular diagnosis of SPG3A, complained subacute sensory-motor symptoms. Spinal MRI disclosed T2-hyperintense lesions at C2, T6 and T4 level, the latter presenting contrast-enhancement. CSF analysis showed oligoclonal bands. She was treated with intravenous high-dose steroids, with symptom resolution. The literature review yielded 13 papers reporting 20 possible cases of MS and HSP. Nine patients (5 M, median age 34) met the 2017 McDonald criteria. Five (25%) received a diagnosis of RRMS and four (20%) of primary progressive MS. Brain MRI showed multiple WM lesions, mostly periventricular. Six of seven cases (85.7%) had spinal cord involvement. Oligoclonal bands were found in 6/8 (75%) patients. Seven patients (77.7%) improved/stabilized on immunotherapy.

Conclusion This is the first description on the association between SPG3A type of HSP and MS. This report adds to the other reported cases of co-occurring HSPs and MS. Although it remains unclear if this association is casual or causal, clinicians should be aware that an HSP diagnosis does not always exclude a concomitant MS.

Keywords Hereditary spastic paraplegia · Atlastin · SPG3A · Multiple sclerosis

Introduction

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous disorders that share the primary feature of a progressive lower extremity weakness and spasticity [1]. Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammatory demyelination [2]. Despite differences in the underlying pathogenetic mechanisms, HSP shares with multiple sclerosis (MS), particularly its primary progressive (PPMS) variant, some clinical features, including the progressive degeneration of the corticospinal tracts. Fewer studies investigated the association between gene variants in HSP-associated genes and MS outcome [3–5] with variable results. Conversely, increasing cases of co-occurrence of HSP and MS, both the relapsing-remitting (RRMS) and the PPMS variants, in the same patient or in the same family, have been described [4, 6–18]. Here, we report a new HSP patient harbouring a pathogenic mutation in *ATL1*/SPG3 and presenting RRMS. We also reviewed the current literature of co-occurring MS and HSP.

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Methods

We searched PubMed and Scopus for articles published up to February 2022. We used the search terms: ("hereditary spastic paraparesis") OR ("hereditary spastic paraplegia*") AND ("multiple sclerosis"), restricting the search to studies published in English. Bibliographies were examined manually for further eligible articles. Duplicate cases were identified whenever possible and, in overlapping cohort cases, only the larger was included. The results were screened independently by two reviewers (GR and MPG) who reached a consensus on potentially eligible articles. Extracted data were reported in a predefined form including sex, age at evaluation, gene mutation and inheritance pattern, age at onset, clinical features, neuroimaging and CSF findings, immunotherapy and outcome. The 2017 McDonalds Criteria for MS [19] were retrospectively applied independently by two reviewers (GR and MPG) to the selected cases.

Results

Case report

We describe the case of a 34-year-old woman presenting HSP due to a pathogenic mutation in the *ATL1* gene (SPG3A form). Her first symptoms appeared at the age of 3 with progressive rigidity of the legs and gait impairment. The mother and the maternal grandfather, uncle and aunt complained of the same symptoms since a young age. At the age of 28, molecular analysis revealed a heterozygous c.715C>T (p.R239C) variant in *ATL1* [20]. At that time, the neurological examination revealed moderate spasticity with spastic gait. A spinal MRI only disclosed a small meningioma at level C6–C7 without significant compression. Brain MRI and electromyography were normal.

During the following years, the spastic paraparesis slowly progressed.

A follow-up brain MRI at the age of 34 disclosed some supratentorial small white matter changes, hyperintense on T2/FLAIR images without contrast-enhancement, some of these showing a mild diffusion restriction (Fig. 1A, B, C, D), not associated with specific symptoms. Two months later, the patient experienced sudden onset of reduced tactile sensation, tingling paraesthesia and dysesthesia, initially confined to her left foot, then spreading to the contralateral limb and ascending just below her breasts. This was associated with a worsening of the gait impairment. Spinal MRI disclosed a contrast-enhancing, T2-hyperintense lesion involving the dorsal midline part of the spinal cord, at T4 level (Fig. 1E, F, G, H). Furthermore, T2 hyperintense lesions without contrast-enhancement were observed at C2 and T6 level. CSF analysis showed mild leucocytosis (19 cells/mmc), increased IgG (10.4 mg/dl; cut-off < 3.4 mg/dl), abnormal IgG index (3.57; cut-off: 0.66) and oligoclonal bands. Infections were excluded, and autoimmunity panels were negative, including anti-AQP4 and anti-MOG antibodies. A MS diagnosis was made, and the patient was treated with intravenous high-dose steroids, with gradual symptom resolution. MRI performed after 6 months showed an improvement of the spinal lesions (Fig. 1M, N). No more attacks occurred during a 2-year follow-up.

The mother of the patient, carrying the same *ATL1* mutation and affected by a pure spastic paraplegia since her childhood, did not disclose white matter lesions at brain MRI.

Literature review

Overall, 13 papers were selected (Fig. 2), and 20 possible cases of MS and HSP were identified (Table 1) [6–18]. These included 6 (30%) cases with reported RRMS, 6 (30%) with reported PPMS, one (5%) reported as CIS, one patient with MRI criteria of dissemination in space and one without MS diagnosis. In the remaining cases, the MS course was not reported. For 8 (40%) cases, there were not enough data to achieve the diagnosis, whereas one case did not meet the criteria for MS. Nine patients (5 M, 4 F, median age 34 years, range 10–49) met the 2017 McDonald criteria for MS [19] and were included in the analysis. Five (25%) received a diagnosis of RRMS and four (20%) of PPMS. HSP-associated mutations were found in SPG4/*SPAST* in 3 cases, SPG2/*PLP1* in further 3, SPG11/*KIAA1840* in 2 and *SPG7* in one individual. Brain MRI was available in all cases, showing the presence of multiple WM lesions, mostly periventricular. The administration of gadolinium was reported in 5 cases and contrast enhancement demonstrated in 4 (80%). Spinal cord involvement was assessed in 7 cases, demonstrating the presence of single or multiple lesions in 6 (85.7%). Oligoclonal band presence was reported in 6 (75%) of the 8 cases for which CSF analysis was available. All cases underwent immune treatment, including iv methylprednisolone (IVMP) during the acute phase in 8 cases and disease-modifying therapies (DMTs), such as interferon 1 beta, teriflunomide (TFN), dimethyl fumarate (DMF), natalizumab (NTZ) or rituximab (RTX) in 5 cases. Seven patients (77.7%) improved or stabilized on immunotherapy, whereas two, treated only with steroids, showed no response.

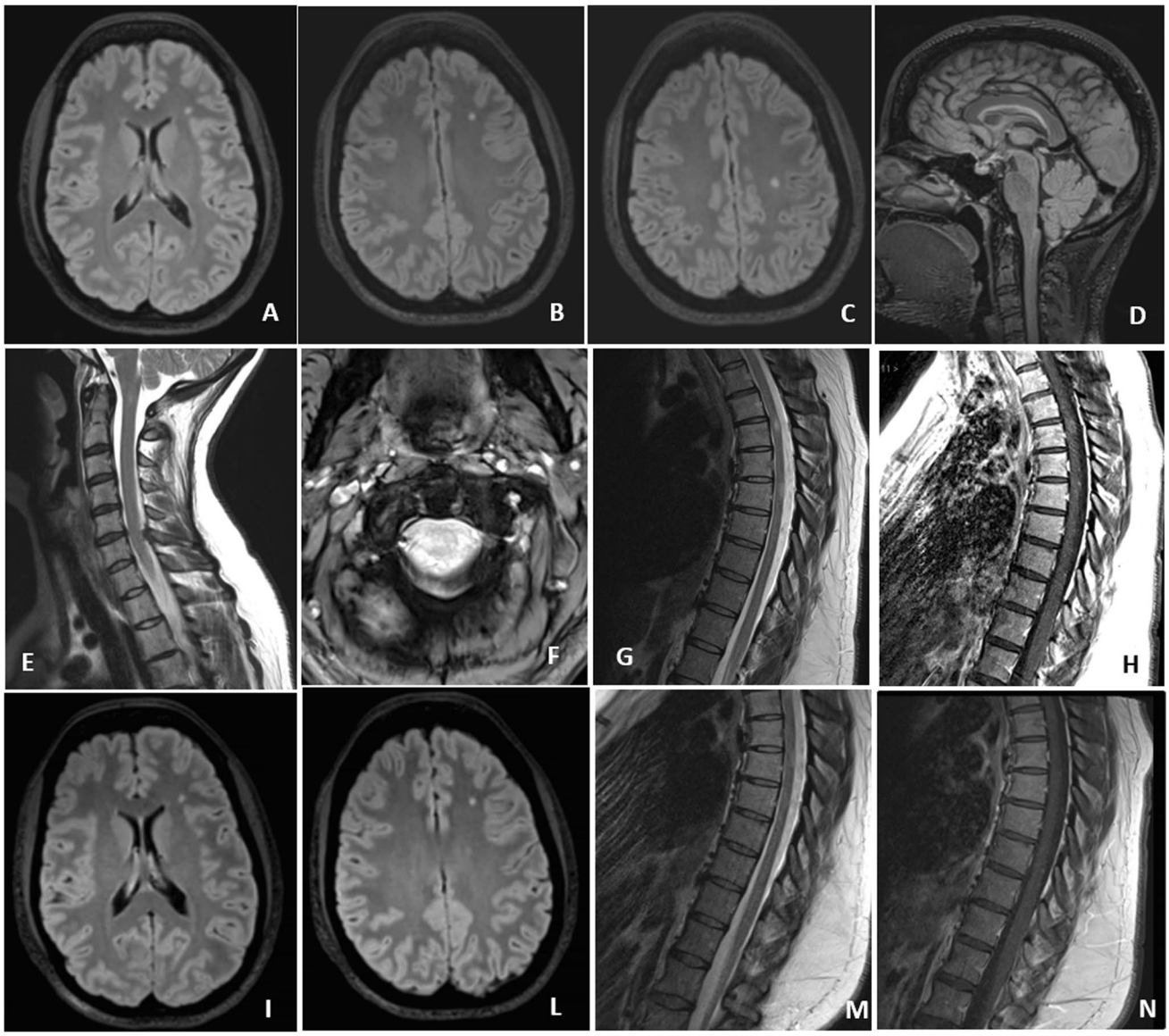

Fig. 1 Brain and spinal cord MRIs. In the upper row, the baseline lesion load is visible. (**A**, **B**, **C**): axial T2-weighted fluid attenuation inversion recovery (FLAIR) images showing little hyperintense deep white matter lesions in the left frontal lobe. **D** Sagittal fluid attenuation inversion recovery (FLAIR) image T2 does not show any abnormal signal in other typically involved structures (corpus callosum, pons, bulbo-medullary junction and cerebellum). In the middle row, spinal cord MRI (2 months later): **E** Sagittal TSE T2-weighted and **F** axial MERGE T2 showing C2 cervical spinal cord lesion on the right medullar side. **G** Sagittal TSE T2-weighed images showing two dorsal lesions at T4 and T6 levels. Swollen spinal cord is visible at T4 level. **H** Sagittal TSE T1-weighted after gadolinium shows pathological contrast enhancement of the most cranial dorsal lesion (T4 level). In the lower row, brain and spinal follow up MRI (8 months later). **I**, **L** Axial T2-weighted fluid attenuation inversion recovery (FLAIR) images showing unchanged small isolated white matter lesion in left frontal lobe. **M**, **N** Spinal cord images showing less swollen medulla with slight reduction of the two dorsal spinal lesions without contrast enhancement. Note the incidental finding of a small meningioma at level C6-C7 (**E**)

Discussion

Our patient presented the classic SPG3A phenotype, with a pure early-onset HSP. SPG3A is caused by mutations in *ATL1* gene on chromosome 14. *ATL1* codes for atlastin, a GTPase protein predominantly expressed in pyramidal neurons and grouped in the dynamin family, involved in many cellular processes, as cytoskeletal function, mitochondrial maintenance and in synaptic vesicle recycling [20]. At the age of 34, the patient experienced a reversible sensory deficit recognized as a MS attack. This diagnosis was supported by the neuroimaging and laboratory findings and further corroborated by the response to IVMP.

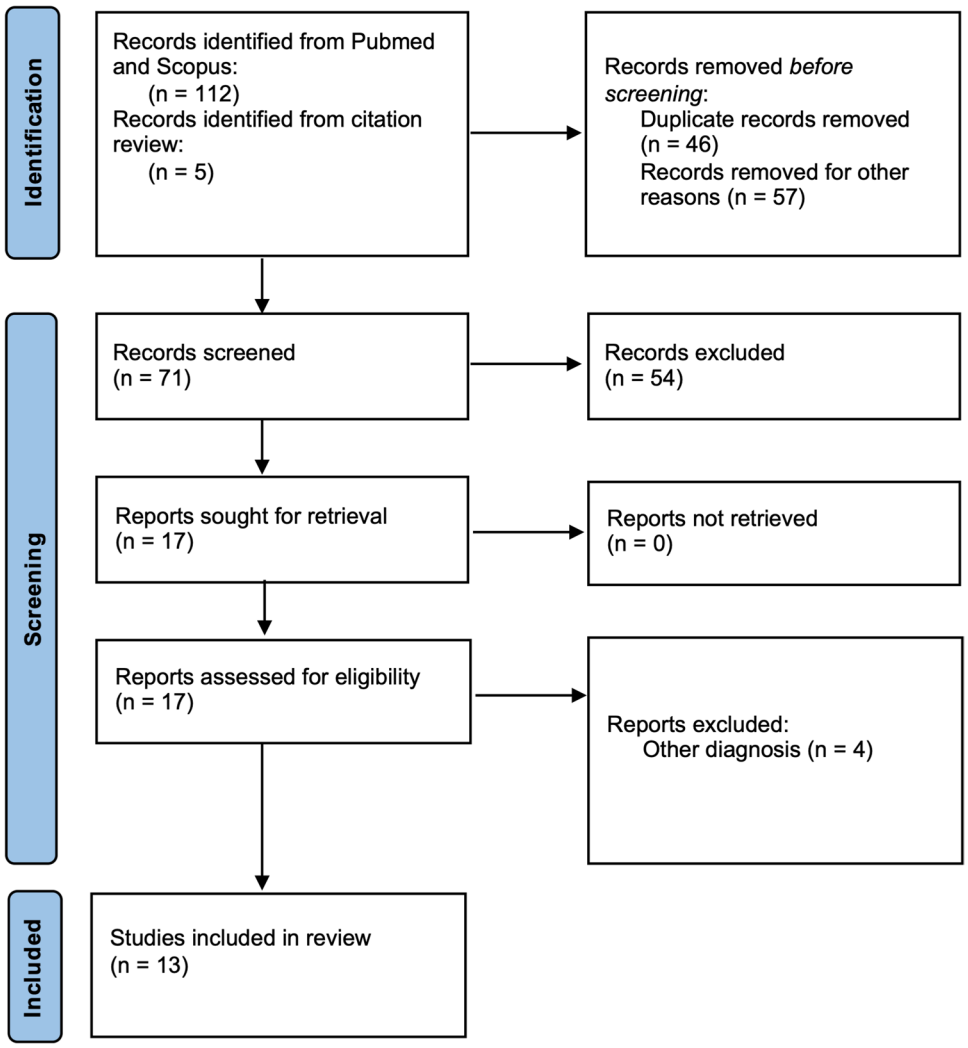

Fig. 2 Flow diagram. Study selection flow chart

A casual association can be possible, although, based on a prevalence of 176×10^{-5} for MS in Italy [21] and of 1.8×10^{-5} for autosomal dominant HSP [22], the association would have a probability of 0.3×10^{-7}. The increasing number of reports in which HSP and MS occur in the same patient or family [4, 6–18], can suggest that this association is more than the result of a chance.

From our literature review, we identified 20 patients with the possible association of MS and HSP [6–18], mostly related to *SPAST* mutations. However, in many cases, there were not enough data to achieve a definite MS diagnosis according to the 2017 McDonald criteria for MS [19]. In other cases [15, 16], the same authors pointed out a MS misdiagnosis due to a mimicry between the two conditions, although one case still met the 2017 McDonalds criteria for MS [16]. A similar misdiagnosis cannot be excluded also in other cases. Indeed, the 2017 McDonalds criteria are highly sensitive but not specific for MS, and misdiagnosis is frequent [23]. Diffused WM hyperintensities on T2-weighted images have been reported in patients with HSP associated with different mutations including genes associated with the SPG11, SPG2, SPG5, and SPG35 subtypes of HSP [24], in some cases leading to a misdiagnosis of MS [15, 16]. Similarly, another reported case with SPG4 HSP met the dissemination in space criteria at brain MRI, although the atypical morphology/distribution of lesions was red flags for an alternative diagnosis [11]. However, such lesions have never been reported in patients with SPG3A [25]. Moreover, oligoclonal bands have been identified also in subjects with Mendelian and mitochondrial neurological disorders [26], and therefore, their presence is not highly specific for MS [27]. However, spinal cord inflammatory lesions were confirmed by MRI in 85% of assessed cases, a finding not reported in HSP [24]. Moreover, 80% of cases with reported MS and HSP undergoing immunotherapy, including ours, presented some

Table 1 Demographic and clinical features of the present and literature cases. The first part of the table reports the cases of MS, whereas the second part reports the two "mimics" cases. Note that one of the latter two met the 2017 McDonalds criteria for MS

Ref.	Family	Patient n	Age, sex	Gene	Disease	Mutation	Inheritance	Age at onset	Clinical features	Reported MS course	Brain MRI	Spine MRI	CSF findings	2017 MS criteria	Immune therapy	Response to immune therapy
Mead SH et al.	1	1	48, F	SPAST	SPG4	1406delT in exon 10	AD	22	Age 22: acute onset of visual disturbance. Age 37: acute loss of balance, dysarthria, and incoordination. Increasing spasticity over the years	RRMS	Large right periventricular focal white matter high signal on T2WI	N/A	OCBs+	Yes	IVMP	Some response
	1	2	50, F	SPAST	SPG4	1406delT in exon 10	AD	25	Spastic paraparesis. Other features: asymmetry of spasticity in the lower limb, distal sensory abnormalities in all four limbs, psychiatric morbidity	PPMS	Frontal focal white matter lesions in patient on T1WI	N/A	OCBs+	Not enough MRI data	No	N/A
Yazici I et al.	1	3	34, M	SPAST	SPG4	c.310_311InsA	AD	32	Episode of tremor of the left leg at age 32 years. At 33 years, right eye vision loss with partial resolution. At 37 years, nystagmus, pyramidal signs, spastic gait, sensory loss noted distally from the T11 level. At 39 years, right hemiparesis. At 40 years, right gaze evoked nystagmus, left VI cn palsy, pyramidal signs, unsteady gait	RRMS	Multiple hyperintense lesions in the deep and periventricular WM on T2WI and FLAIR. Third episode: lesions with CE at the centrum semiovale and corona radiata.	First: normal. Second: T10–11 lesion with CE	N/A	Yes	IVMP, IFNb1B	Improvement with IVMP. Stabilization on IFNb1B
	1	4	N/A, F	N/A		N/A		N/A	Patient's mother with diagnosis of MS and epilepsy	N/A	N/A	N/A	N/A	Not enough data	N/A	N/A
	1	5	N/A, F	N/A		N/A		N/A	Patient's sister diagnosed with MS	N/A	N/A	N/A	N/A	Not enough data	N/A	N/A
	1	6	N/A, M	N/A		N/A		N/A	Patient's maternal cousin diagnosed with MS	N/A	N/A	N/A	N/A	Not enough data	N/A	N/A
Boucher JJ et al.	1	7	40, M	SPAST	SPG4	c.926G>A, p.(Arg309His)	AD	39	Left leg weakness and incomplete bladder emptying with progression over time	PPMS	Periventricular and juxtacortical WM hyperintensities	Area of T2 hyperintensity at C4/C5, predominantly on the right	Mildly elevated IgG index (0.77 mg/day). OCBs+	Yes	RTX	Stable

Table 1 (continued)

Ref.	Family	Patient n	Age, sex	Gene	Disease	Mutation	Inheritance	Age at onset	Clinical features	Reported MS course	Brain MRI	Spine MRI	CSF findings	2017 MS criteria	Immune therapy	Response to immune therapy
Bellinvia et al.	1	8	39, M	SPG7	SPG7	c.2162A>G/p.Asn721Ser	AR	35	Insidious onset of unsteady gate. NE: spastic-ataxic gait, diffuse hyperreflexia, reduced vibratory sensation, positive Romberg's test and bilateral nystagmus	Active PPMS	Diffuse WM areas of hyperintensity in the brainstem, corona radiata and centrum semiovale, some with CE	Non-enhancing lesions at the cervical and dorsal spinal cord	Elevated IgG Index (0.86) and OCBs+	Yes	IFNb1B; TFN, DMF; IVMP	Stabilization on DMF; improvement with IVMP
Laurencin C et al.	1	9	19, M	SPG11	SPG11	c.5255delT/p.Phe1752SerfsX86 (in exon 30) and c.6754+2_6754+3dupTG (in intron 36)	AR	10	Progressive paraparesis with mental retardation and dysarthria since age 10. At age 19: subacute worsening of lower-limb spasticity and right hemiparesis. At age 20: subacute aggravation of a walking disorder and lower-limb spasticity. Four weeks later, new subacute episode of walking disability	RRMS	TCC and ears of the lynx sign. Multiple periventricular and infratentorial WM hyperintensities on T2-WI. No CE. Second episode: new T2 cerebellar WM lesions. No CE.	First episode: large C3–C4 T2 lesion with edema and CE. Second episode: new T2 WM lesion in the cervical spinal cord, without CE Third episode: new spinal cord lesion in T11, with CE	Both episodes: increased protein levels	Yes	IVMP; TFN; NTZ	Improvement with IVMP. Stabilization on NTZ
Maggi P et al.	1	10	68, N/A	SPAST	SPG4	N/A	AD	N/A	Limb weakness	N/A	Multiple lesions respecting the MRI DIS 2017 criteria	N/A	OCBs-	DIS MRI criteria	None	N/A
Dürr A et al.	1	11	42, F	SPAST	SPG4	N/A	AD	26	Leg spasticity, relapsing episodes of motor weakness	N/A	"Suggestive of MS"	N/A	OCBs+	Not enough data	N/A	N/A

Table 1 (continued)

Ref.	Family	Patient n	Age, sex	Gene	Disease	Mutation	Inheritance	Age at onset	Clinical features	Reported MS course	Brain MRI	Spine MRI	CSF findings	2017 MS criteria	Immune therapy	Response to immune therapy
Rubegni A et al.	1	12	29, F	PLP1	SPG2/ PMD	c.210T N G/p.Tyr70*	X-linked	10	Progressive spastic paraparesis and ataxia. Late teens: bipolar mood disorder. She also presented urinary urgency. Age 28 years: two episodes of optic neuritis.	PPMS	Diffuse and confluent hyperintensity on T2WI and FLAIR in the deep and periventricular WM of both cortical hemispheres and multiple focal lesions which had increased in number over the 7 years	Patchy and confluent hyperintensities in the spinal cord WM without CE	CSF at 22 y: OCBs+ and increased IgG index	Yes	IVIM	Yes; resolution of ON
	1	13	53, F	PLP1	SPG2/ PMD	c.210T N G/p.Tyr70*	X-linked	adolescence	Moderate progressive cognitive impairment and urinary incontinence	PPMS	Diffuse confluent high signal intensity in the deep and periventricular WM on T2WI and FLAIR without CE	N/A	Negative OCBs-	Not enough MRI data	N/A	N/A
Warshawsky I et al.	1	14	49, F	PLP1	SPG2/ PMD	Leu30Arg (c.89T G)	X-linked	39	Progressive gait disturbance associated with spasticity, hyperreflexia, muscle spasms, nocturia and dysarthria	PPMS	Areas of increased signal intensity in the deep WM	Scattered lesions in the lower pons, medulla, and cervical cord	OCBs+ and increased IgG index	Yes	IVIM	No
Gorman MP et al.	1	15	10, M	PLP1	SPG2/ PMD	c.409C>T	X-linked	10	Cognitive impairment, intermittent diplopia and clumsiness, after an upper respiratory infection. At age 11: unsteady gate, dysmetria and nystagmus. Few months later: right leg weakness and unsteady gate. At age 13 years: episode of nystagmus, dysmetria and unsteady gate	N/A	Multifocal hyperintensity on T2WI in the centrum semiovale, corona radiata, brainstem, and periventricular WM. MRI at age 11 years: new subcortical, periventricular, and brainstem WM lesions, several with CE. Further MRI: resolution of several old lesions, but new lesions in the medulla, thalamus	Several lesions	Pleocytosis (8 WBC) and OCBs+	Yes	IVIM, oral steroids; IFN-beta1a	Resolution of nystagmus and ataxia, and brain MRI lesion changes with IVMP. New episode while on IFN

Table 1 (continued)

Ref.	Family	Patient n	Age, sex	Gene	Disease	Mutation	Inheritance	Age at onset	Clinical features	Reported MS course	Brain MRI	Spine MRI	CSF findings	2017 MS criteria	Immune therapy	Response to immune therapy
Varghaei P et al.	1	16	N/A	SPAST	SPG4	p.(Lys414Lys)	AD	6 to 10	Lower extremity spasticity, hyperreflexia and extensor plantar responses	N/A	N/A	N/A	N/A	Not enough data	N/A	N/A
	2	17	N/A	SPAST	SPG4	p.(Lys414Lys)	AD	61 to 65	Progressive walking difficulties	N/A	N/A	N/A	N/A	Not enough data	N/A	N/A
	2	18	N/A	SPAST	SPG4	p.(Lys414Lys)	AD	21 to 25	Progressive walking difficulties. Between age of 31 and 35 episode of diplopia	CIS	N/A	N/A	OCBs+	CIS	IVMP	Resolution of diplopia
Present case	1	19	34, F	ATL1	SPG3A	c.715C>T (p.R239C)	AD	3	Progressive rigidity of the legs and gait impairment. At age 24, sudden onset of reduced tactile sensation, tingling paresthesias and dysesthesia.	RRMS	Some supratentorial small WM changes, hyperintense on T2/FLAIR images without CE	T2WI-hyperintense lesion involving the dorsal midline part of the spinal cord, at T4 level with CE. Further T2 hyperintense lesions without CE at C2 and T6 level	Mild leukocytosis, abnormal IgG index, OCBs+	Yes	IVMP	Yes
Romagnolo A et al.	1	20	22, F	SPG11	SPG11	c.4604_4605insC andc.5989_5992delCTGT	AR	22	Subacute onset of spastic paraparesis followed by falls, 'cramps', urge incontinence and slight memory disturbances.	None	FLAIR hyperintense confluent lesions, without CE, in the frontal, parietal and peritrigonal regions bilaterally. Atrophy and TCC	Normal	Normal	No	No	N/A

Table 1 (continued)

Ref.	Family	Patient n	Age, sex	Gene	Disease	Mutation	Inheritance	Age at onset	Clinical features	Reported MS course	Brain MRI	Spine MRI	CSF findings	2017 MS criteria	Immune therapy	Response to immune therapy
Mukai M et al.	1	21	24, F	SPG11	SPG11	c.208C>A, c.2450C>T and c.6809_6810delCT	AR	15	Left-side hemiparesis, progressive cognitive impairment. At age 20 and 22 years: facial nerve palsy and bilateral oculomotor disturbance. New episodes with a wide variety of symptoms, including sensory disturbance and weakness	RRMS	TCC and scattered WM lesions around the ventricles on T2WI. At 22: new lesions in the white matter and brain stem; one showed ringed CE. New lesions appeared in subsequent episodes. Typical findings of MS (periventricular ovoid lesions perpendicular to the ventricles, Dawson's fingers, juxtacortical lesions, and T1 black holes) not detected.	Normal	Normal IgG index, OCBs-	Yes	IVMP; oral steroids	No

AD autosomal dominant, *AR* autosomal recessive, *CE* contrast enhancement, *CIS* clinically isolated syndrome, y years, *CSF* cerebrospinal fluid, *DMF* dimethyl fumarate, *F* female, *IFN1b* interferon 1 beta, *IVMP* intravenous methylprednisolone, *M* male, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *N/A* not available, *NTZ* natalizumab, *OCBs* oligoclonal bands, *PPMS* primary progressive MS, *RRMS* relapsing remitting MS, *RTX* rituximab, *TCC* thin corpus callosum, *T2WI* T2-weighted image, *TFN* teriflunomide, *WM* white matter

degree of clinical improvement or disease stabilization, supporting the presence of a concomitant ongoing inflammatory process.

It has been demonstrated that patients with PPMS and SPMS are enriched for HSP-related mutations causing axonal injury, which could contribute to disease evolution in progressive MS [4, 5]. On the other hand, a broader link between inflammation and neurodegenerative diseases has been described [28]. According to this, misfolded proteins or nucleic acids in non-physiological compartments act as damage-associated molecular patterns (DAMPs), activating microglia and other cell types that express protein recognition receptor (PPR). This eventually triggers inflammatory events that contribute to neuronal dysfunction and death. A similar process could also take place in HSPs, where chronic neuronal damage releases antigens, possibly triggering an autoimmune response. Notably, MS has been described in association with other genetic diseases (e.g. neurofibromatosis and LHON) [29, 30]. This would be in line with the "intrinsic model" of MS pathogenesis, which hypothesises that the initial event that triggers autoimmunity happens inside the CNS and leads to release of antigens peripherally.

In conclusion, our case adds to the literature supporting the need to further investigate a possible pathogenic link between HSP and MS. Furthermore, these cases offer further food for thought, that is, in a patient suffering from hereditary spastic paraplegia or other neurodegenerative disease, one must not make the mistake of underestimating the appearance of new or atypical symptoms.

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Author contribution (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

MPG: 1C, 3A, B; EM: 1C, 3A, B; FB: 1C, 3B; CT: 1B, 3B; FMS: 2C, 3B; RL: 1B, 3B; GR: 1A, 1B, 1C, 3B

Declarations

Conflict of interest Liguori R: consultation fees (Alfasigma, Amicus Therapeutics s.r.l.), lecture fees (SIMG Service, Adnkronos Salute unipersonale s.r.l., Fondazione Società Italiana di Neurologia, LT3 s.r.l., First Class s.r.l.), advisory board fees (Argon Healthcare s.r.l., Editree Eventi s.r.l., PREX s.r.l., LT3 s.r.l.), congress chair fees (DOC Congress s.r.l.), and scientific meeting organization chair fees (First Class s.r.l., I & C s.r.l.).
Other authors: No disclosures.

Ethics approval This was a retrospective case report and did not require IRB approval. Written declaration of patient consent was obtained from the patient and family. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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