Hereditary spastic paraplegia caused by the *PLP1* 'rumpshaker mutation'

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ABSTRACT

Background Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurodegenerative disorders characterised by progressive spasticity and weakness in the lower limbs. Mutations in *PLP1* on the X chromosome cause spastic paraplegia type 2 (SPG2) or the allelic Pelizaeus—Merzbacher Disease (PMD). The *PLP1* protein is a major myelin protein involved in stabilisation and maintenance of the myelin sheath. The function of the protein has been studied in the rumpshaker mouse, which is a model of SPG2/PMD.

Objective To characterise the phenotype of patients with the 'rumpshaker mutation.'

Patients A family with HSP caused by the 'rumpshaker mutation.'

Results The patients showed nystagmus during infancy and had early onset of HSP. They had normal cognition, and cerebral MRI showed relatively unspecific white matter abnormalities on T2 sequences without clear progression. Urinary urgency was reported among the female carriers. MRS of both patients showed increased myo-inositol in the white matter, while decreased N-acetylaspartate was found exclusively in the oldest patient. All evoked potential examinations were compatible with severe central demyelination, while no signs of peripheral demyelination or axonal degeneration were found. ^{18}F-FDG-PET scans were normal.

Conclusion The phenotypes of the patients reported here are the mildest described to be caused by the rumpshaker mutation and represent the mildest form among the spectrum of *PLP1* related disorders. No definite symptoms in the female carriers could be ascribed to the mutation. These data suggest the pathology to be an underlying dysmyelinating disorder in combination with a central axonal degeneration.

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative disorders characterised by slowly progressive spasticity and weakness of the lower limbs in the pure form and additional neurological symptoms and signs in the complex form.[1] Inheritance can be autosomal dominant, autosomal recessive or X linked. At present, four loci linked to HSP are located on the X chromosome.[2–5] *L1CAM* and *PLP1* are the genes associated with SPG1 and SPG2 respectively, whereas the gene associated with SPG16 and SPG34 are presently unknown.

Mutations in *PLP1* give rise to the allelic diseases spastic paraplegia type 2 (SPG2) and Pelizaeus—Merzbacher disease (PMD). These diseases can be seen as a spectrum in which pure SPG2 is the mildest form, and PMD form 0 or 'connatal' is the most severe form. SPG2 is characterised by spastic gait, autonomic dysfunction, normal intelligence and normal lifespan, whereas PMD form 0 includes neonatal stridor and nystagmus, seizures, severe hypotonia without neuromotor acquisitions followed by spastic quadriparesis, severe cognitive impairment and death before 10 years of age.[6]

Female carriers of *PLP1* mutations can display early-onset symptoms which improve over time or slowly progressive mild HSP with late onset. The probability of females being symptomatic rises if male relatives are only mildly affected or if the mutation in the family is a nonsense or null mutation.[7]

The PLP1 protein and its splice variant DM20 have the highest expression in oligodendrocytes and constitute 50% of the myelin proteins. PLP1 is involved in stabilisation and maintenance of the myelin sheath, and it plays a major role in axono-myelin interactions, whereas DM20 is assumed to be involved in oligodendrocyte maturation.[8 9] The function of the protein has been studied in a range of spontaneous and genetically engineered animal models including the spontaneous mutant rumpshaker mouse (*rsh*). The *rsh* displays a relatively benign phenotype with tremor and preserved lifespan.[10] It has an Ile187Thr mutation in *Plp1* (known as 'the rumpshaker mutation'),[11] corresponding to a mutation later found in a single family with HSP.[12 13] *Rsh* is therefore considered to be a good model of mild PMD/SPG2.

We identified the rumpshaker mutation in *PLP1* in a family with X linked HSP, and we report clinical and paraclinical data of affected males and female carriers from this family and compare the findings with previous reports of this specific mutation in humans and mice.

METHODS

Patients

A family displaying a possible X linked recessive inheritance of HSP with two affected male cousins (figure 1) was referred to the Section of Neurogenetics, Department of Cellular and Molecular Medicine, University of Copenhagen. The family was clinically examined, and blood samples were obtained.

The two affected male cousins underwent electrophysiological investigation, neuropsychological examination, MRI, MRS and ^{18}F-FDG-PET-scanning of the brain. Three female carriers of the

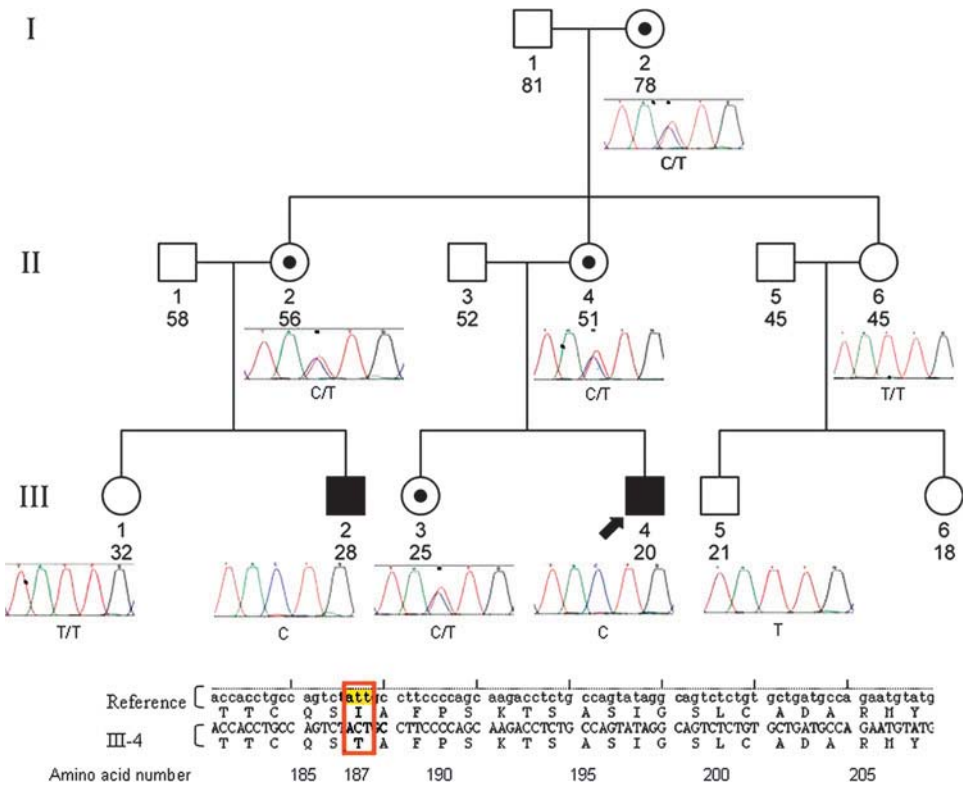

Figure 1 Pedigree of the Danish family with PLP1 mutation. Open circle or square: asymptomatic. Filled square: affected by HSP. Dot in a circle: carrier of the PLP1 mutation. The first number beneath the symbol indicates the number of the individual in the generation. The second number beneath the symbol indicates the age of the individual. The arrow indicates the proband. The figure also shows the electropherograms for the genotyped individuals and the missense mutation in the sequence.

mutation underwent neuropsychological examination, MRI and MRS. The study was approved by the local ethics committee, and all participating individuals gave informed consent.

Mutation detection

Genomic DNA was extracted from blood using Puregene DNA Purification Kit (Gentra Systems, Minneapolis, Minnesota). Linkage mapping of the X chromosome was performed using Abi Prism Linkage Mapping Sets v2.5 (Applied Biosystems, Foster City, California) with a resolution of 10 cM according to the manufacturer's recommendations. Seventeen additional microsatellite markers were included between the centromere and Xq23. Linkage and haplotype analysis were performed with Genehunter software v1.1.

Amplification of the 7 *PLP1* gene coding exons and their intron/exon boundaries was performed as previously reported.[6] Sequence reactions were performed with the BigDye v1.1 Terminator (Applied Biosystems) using the PCR primers and analysed using the Sequence Navigator software after migration on a capillary ABI PRISM 3100 Genetic Analyser (Applied Biosystems, Foster City, California, USA).

Neuroimaging and spectroscopy

Magnetic resonance (MR) studies at 1.5 T Siemens Vision scanner included T_1-, T_2- and diffusion-weighted MR imaging including the calculated apparent diffusion coefficient (ADC) images, supplemented by localised proton MR spectroscopy. MR spectra (TE=20 ms, repetition time=3000 ms) were sampled from volumes of interest in occipito-parietal primarily white matter (WM), mid-occipital primarily grey matter (GM), and from the centrum semiovale in a location of affected white matter in HSP. Metabolites were quantified by the user-interaction-independent postprocessing LCModel[14] as previously described,[15] and normal controls from this study were used as reference for the HSP patients. N-acetylaspartate (NAA), total choline (Cho), total creatine (Cr) and myo-inositol (mI) concentrations deviating more than 2 SD from normal were reported.

PET

The distribution of relative regional cerebral glucose metabolic rate (rCMRglc) was measured using FDG PET scanning. PET scans were performed with a GE-Advance scanner operating in 3D-acquisition mode. Each patient received an intravenous bolus injection of approximately 200 MBq FDG while resting. After 30 min, a 10 min transmission scan was performed for attenuation correction followed by a 10 min emission scan. Images were fused to the T1 and T2 weighted MR scans. In addition to visual analysis, quantitative 3-D stereotactic surface projection (SSP) analysis (Neurostat) was employed, comparing each patient to a normal material.[16]

Electrophysiology

Both patients underwent neurophysiolgical examinations including visual-evoked potential (VEP) with pattern-reversal stimulation of 18 mm squares at 2 Hz, and recording at Oz. Somatosensory-evoked potentials (SSEP) were evoked by stimulating the median and tibial nerve with surface elctrodes at 1½ Hz at 1½ X motor threshold and recording, for the median nerve stimulation, at elbow, Erbs point, C7 and Cz and for tibial nerve stimulation at popliteal fossa, Th12 and Cz. Motor-evoked potentials (MEP) were evoked in muscles in upper and lower extremities by stimulating the cortex (just lateral to vertex) with a 90 mm round coil (MagStim) with at least 60% of maximal stimulation output. Root stimualtion was performed by the stimulating at C7 and L4/L5 at 100% of maximal stimulation output. Peripheral nerve examination was performed by using surface electrode technique. The median, tibial, peroneal and sural nerves were examined. Quantitative electromyography (EMG) examination was performed in the anterior tibial muscle by collecting at least 20 different muscle action potentials

(MUP) with a concentric emg needle electrode. The mean duration and mean amplitude of the collected potentials were calculated, and the maximal interference pattern was observed and spontanous activity was looked for in at least five different electrode positions. Brainstem auditory-evoked potentials (BAEP) were evoked only in one patient (III4) by 10 Hz click stimulation at 100 dB and recording at Cz and C7.

Neuropsychology

The five individuals were all tested with a comprehensive neuropsychological battery. The following tests were administered:

general intellectual functioning: vocabulary and Information from Wechsler Adult Intelligence Scale (WAIS);

memory: Selective Reminding Test and Rey Complex Figure Test (3 min recall);

executive functions/psychomotor speed: Trail Making Test part A and B, Symbol Digit Modalities Test, Stroop Interference Test, Wisconsin Card Sorting Test, continuous subtraction (100–7), Digit span;

visuospatial functions: Rey Complex Figure Test (copy) and Block Design (WAIS);

language: verbal fluency (s-words and animal names in 1 min);

abstract reasoning: similarities (WAIS), Picture Arrangement (WAIS), Raven's Progressive Matrices Advanced (set 1), Picture Completion (WAIS III) and Matrices (WAIS III). Test performances were compared with age-adjusted normative data.

RESULTS

Mutation detection

Linkage analysis showed Z_{max}=1.02 between markers DXS990 and DXS1105, a region of 14 Mb including the *PLP1* gene, and haplotype analysis did not exclude *PLP1* as a potential gene candidate. Sequencing of the *PLP1* coding region revealed a c.560 T→C transition in the third exon in the two affected male cousins and in four female carriers (figure 1). The mutation is predicted to result in an amino acid change from isoleucine to threonine in position 187 in the PLP protein (p.Ile187Thr) and corresponds to the previously reported 'rumpshaker mutation.'

Patients

The pedigree of the family with the *PLP1* p.Ile187Thr mutation is shown in figure 1. A clinical synopsis of medical history and clinical signs is given for the patients in table 1 and for the female carriers in table 2. Nystagmus and hypotonia was noticed for both patients during infancy. They acquired independent walking around 2 years of age, developed a spastic paraplegia around age 3 and lost independent ambulation at 8 and 15 years of age, respectively. Both had school performances in the normal

Table 1 Medical history and neurological examination of the two patients

			Patient III2	Patient III4
Medical history	Birth	Delivery	Normal at term	Normal, 10 days after term
		Birth weight	4050 g	4200 g
		Malformations		Syndactyly of second and third toe bilaterally and swimming web between third and fourth finger on the left hand
	Motor milestones	Sitting independently	8 months	8 months
		Crawling	13 months	13 months
		Standing with support	14 months	14 months
		Walking independently	22 months	27 months
	Other symptoms	Hypotonia noticed	At birth	5 weeks old
		Appearance/disappearance of nystagmus	Birth/3 years	5 months/2 years
		Appearance of spasticity	3 years	4 years
		Appearance of strabismus	3 years	8 years
		Appearance of double vision and impaired vision		8 years
		Appearance/disappearance of dystonia		15 years/16 years (left foot)
		Loss of independent gait	15 years	8 years
	Operations	Rhizotomy performed	15 years	8 years
		Achilles tenotomies bilaterally performed	7 and 9 years	10 years
	Education	School performances	Normal	Normal
		Finished education	2 years of education in the office business	Higher technical examination programme
		Profession	IT supporter	Under education
Neurological examination	Head	Age at examination	28	20
		Dysarthria	+	+
		Strabismus	Left eye	Right eye
		Eye movements	Normal	Slightly saccadic eye movements and a discrete horizontal nystagmus at gaze to the right
	Upper limbs	Strength and tone	Normal	Normal
		Tendon reflexes	Hyperactive	Hyperactive
	Lower limbs	Strength and tone	Diminished	Diminished
		Patellar reflexes	Absent	Absent (right)/hyperactive (left)
		Achilles tendon reflexes	Absent (right)/clonus (left)	Hyperactive (right)/absent (left)
		Plantar reflexes	Extensor	Extensor
	Other	Sensibility	Vibration sense diminished below chest	Vibration sense diminished below ankle
		Gait	Performed with two crutches/wheelchair	Performed with two crutches/wheelchair

Table 2 Symptoms and signs in the female carriers

		Carrier I2	Carrier II2	Carrier II4
Symptoms		Urinary urge and stress incontinence during 20 years	Mild urinary urgency and stress incontinence	
Profession		7 years in school, no formal education, took care of children	Hair dresser	Nurse
Neurological examination	Age	78	56	51
	Gait	Normal	Normal	Normal
	Patellar reflexes	Normal	Normal	Normal
	Achilles reflexes	Absent	Normal	Normal
	Plantar reflexes	Atypical bilaterally	Normal	Normal
	Vibration sense	Diminished below ankles	Normal	Normal

range. Two female carriers had urinary urgencies around 50 years of age as the only complaint.

MR imaging and MR spectroscopy of the brain

Data are summarised in table 3. Patient III4 had an MRI of the central nervous system performed at the local hospital at 7, 10 and 16 years of age (figure 2). At age 7, symmetrical, periventricular WM lesions were visible without clear progression over the years. Atrophy in terms of marked Virchow–Robin spaces was only visible at 20 years of age. Patient III2 had mild T2 hyperintensities with a more diffuse distribution in the cerebral WM (figure 2). MRI of the three female carriers showed no noticeable abnormalities. No FLAIR sequences were available. ADC was increased in abnormal WM signal regions but not in normal-appearing WM. Myoinositol was significantly increased in the MR spectroscopies in both patients. Lactate was not detected (figure 3) in any of the patients, not even in the most severely affected location in the centrum semiovale.

^{18}F-FDG-PET-scanning in affected patients

The ^{18}F-FDG-PET-scanning in both patients were normal.

Neuropsychology

Patient III2, patient III4, carrier II2 and carrier II4 had performances within the normal range. Carrier I2 had significant impairments on complex executive tests (Trail Making Test B and Stroop Interefference) and some tests for abstract reasoning (Raven's Advanced Matrices and Similarities). Her copy (and therefore also the recall) of the Rey Complex Figure Test was impaired. Other test performances were within the normal range. Thus, the neuropsychological test results for this individual demonstrated cognitive impairment in executive functions but no general dementia. All patients and carriers showed normal behaviour without any signs of frontal-lobe dysfunction.

Electrophysiology in patients (III2 and III4)

In both patients, VEP examination showed a severely prolonged latency to the cortical responses which were of normal amplitude. At stimulation of the median as well as the tibial nerve, the SSEP examination did in both cases show severely prolonged central conduction time or absent cortical responses, while peripheral responses were of normal latency and amplitude. In the oldest patient (III2), MEP examination also showed severely prolonged central conduction time to muscles in both arms and legs, while the root stimulation evoked muscle responses with normal latency and amplitude. The MEP examination of the youngest patient (III2) showed less pronounced changes, but the central conduction time was clearly prolonged to the responses in the left arm and leg. Examination of the peripheral nerves showed normal conduction velocity of motor and sensory fibres, and all responses were of normal amplitude. EMG examination revealed no spontaneous denervation activity, the mean duration and amplitude of MUPs were normal, and there were thus no signs of acute or chronic denervation. The maximal interference pattern was of normal amplitude but revealed that the patient had difficulties in exerting a constant maximal contraction, which is a typical finding in central lesions. BAEP were abnormal, showing increased central latency compatible with central demyelinating disease. Electrophysiological examination was not performed in the female carriers.

Table 3 Summary of present MRI findings and MRS results deviating more than two SD from normal

		Carrier I2	Carrier II2	Carrier II4	Patient III2	Patient III4
Age		78	56	51	28	20
MRI		Age-related changes with a few small deep WM lesions and slight central atrophy, no more than expected for age. Normal ADC in the WM: 79 GY.	An excess of small WM lesions, but no atrophy. Normal ADC in the WM: 81 GY.	Normal MR imaging. Normal ADC in the WM: 83 GY.	Periventricular WM lesions, multiple small deep WM lesions, slight cortical atrophy. Marked Virchow–Robin spaces. ADC was increased in the WM lesions (139 GY) but normal in the normal appearing WM (80 GY).	Periventricular WM lesions, marked Virchow–Robin spaces, but otherwise no atrophy. ADC was increased in the WM lesions (109 GY) but normal in the normal appearing WM (80 GY).
MRS	GM	No deviating results	Cr: +13%(+2.1 SD) ml: +42% (+3.3 SD)	NAA: −10% (−2.4 SD)	NAA: −11% (−2.7 SD)	NAA: +10% (+2.4 SD) Cr: +18% (+2.8 SD)
	WM	No deviating results	NAA: −14% (−2.3 SD)	No deviating results	NAA: −10% (−2.4 SD) Cr: +22% (+2.3 SD) Cho: +22% (+2.3 SD) ml: +55% (4.5 SD)	ml: +26% (+2.1 SD)

ADC, apparent diffusion coefficient; Cho, total choline; Cr, creatine; GM, grey matter; ml, myo-inositol; NAA, N-acetylaspartate; WM, white matter.

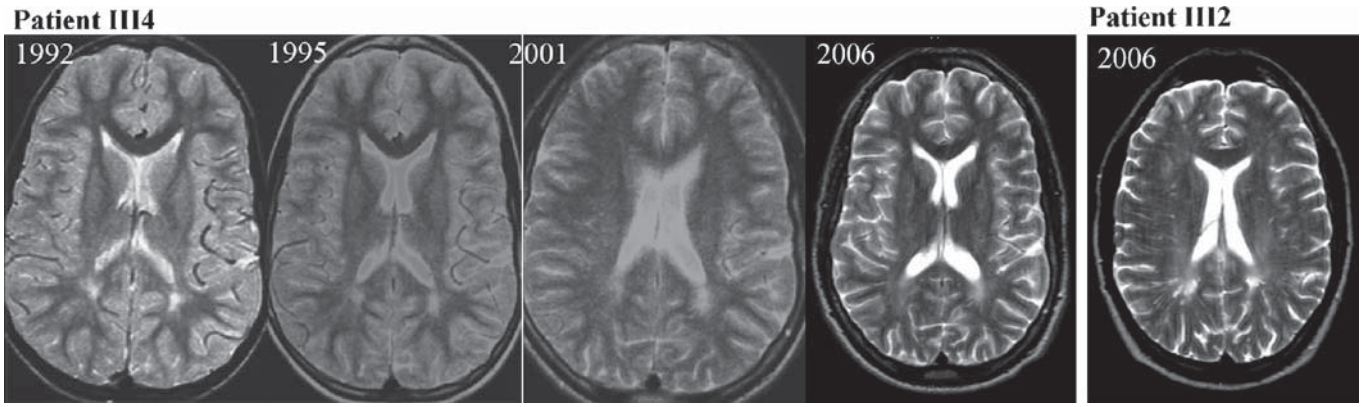

Figure 2 T2 weighted MRI of patient III2 and III4. Patient III4 was 7 years of age in 1992, 10 years of age in 1995 and 16 years of age in 2001. Patient III2 was 28 years of age, and patient III4 was 20 years of age in 2006.

DISCUSSION

Only one family with SPG2 caused by the rumpshaker mutation has previously been described.[12 13 17–19] In that family, clinical evaluation were possible for 10 among the 17 reported affected males at a mean age of 36±27 years. The level of handicap in the affected patients tended to converge after the third decade, suggesting a more severe progressive neuronal degradation than in patients with disease causing mutations in *SPAST* or *SPG3A* and with an onset before 10 years of age.[20 21] The phenotype in the patients described in the present study (table 1) corresponds to the mildest phenotype of the first reported family. The normal cognitive functions are reflected by the normal ^{18}F-FDG-PET scans. No specific phenotype of the female carriers reported here could be ascribed to the carrier status of the *PLP1* mutation in either the clinical or the paraclinical investigations. It remains elusive, though, whether the bladder dysfunction in the two carriers and the dysexecutive function in the oldest carrier could be due to the carrier status. Previously, no female carriers of the rumpshaker mutation have been described as symptomatic.[13]

The consecutive MRIs of the brain from patient III4 (figure 2) showed patchy areas of increased T2 intensity in the periventricular WM without clear progression. At 20 years of age, slight atrophy in terms of marked Virchow–Robin spaces was present. In patient III2, representing a later stage of the disease, the patchy areas of increased T2 intensities were more diffuse, but no previous scan was available to evaluate a potential progression. A corresponding patchy pattern was found on MRI from a 3.5-year-old boy, belonging to the family originally reported to carry the rumpshaker mutation,[18 22] but the hyperintensities were more pronounced and diffuse. These findings were associated with a more severe phenotype including delay in learning capacities. The MRI findings suggest a heterogeneous, patchy dysmyelinating process, reflecting the variable phenotypes caused by the rumpshaker mutation.

Initial absence of diffuse T2 lesions might have delayed the diagnosis of a dysmyelinating process in patient III4. However, the increased latency/central conduction time observed in the VEPs, BAEPs, MEPs and SSEPs in our patients is compatible with a dysmyelinating disease and strongly argues for analysis of *PLP1*. Interestingly, the BAEPs and VEPs were reported to be normal in the previously mentioned 3.5-year-old boy also carrying the rumpshaker mutation.[22] Extensive absence of myelination of the lateral and ventral corticospinal tracts and of the dorsal and ventral spinocerebellar tracts have been reported at autopsy of a 63-year-old patient with the rumpshaker mutation.[17] Correspondingly, a dysmyelination process in terms of axons with no myelin sheaths or abnormally thin myelin sheaths has been described in *rsh*.[10] Later in life also, axonal degeneration has been described in *rsh*.[23] Considering the relatively mild phenotype, more HSP patients compatible with X linked inheritance, early onset and unspecific mild WM abnormalities on MRI might be candidates for *PLP1* mutation screening, especially when supported by increased central conduction time in evoked potentials, which is indicative of a central demyelinating (or dysmyelinating) disease.

MRS data from the patients are difficult to interpret. Both patients had raised levels of mI in the white matter indicating gliosis[24] consistent with the finding of increased glia cell number and density in *rsh*.[10] Patient III2 also had reduced NAA and raised Cr and Cho in the white matter, while the levels of these metabolites were within the normal range in patient III4. Previously, MRS data on metabolite ratios from the 3.5-year-old affected boy with the rumpshaker mutation was published,[22] but differences between methods make the results difficult to compare. The increase in Cho observed in patient III2 is comparable with other demyelinating leucodystophies[25] and represents a changed membrane turnover as seen when membranes break down, and it is in contrast to the observed decrease in Cho in PMD where myelin is not formed properly.[9 26] NAA is mainly found in neuroaxonal tissue and the reduction in this metabolite seen in patient III2 corresponds to the neuronal loss found at autopsy of a patient with the rumpshaker mutation.[17] Axonal degeneration has been reported in the longest tracts of the *rsh*,[23] while human and mice with null-mutations in *PLP1/Plp1* show more prominent axonal degeneration.[8] MRS has previously been performed on non-rumpshaker mutation patients with PMD, SPG2 and female carriers, but the reports have been contradictory, especially with respect to the measures of NAA.[8 22 26–30] The controversy possibly reflects the fact that the patients carry different mutations which exert their effects in different ways despite involving the same gene. Axonal degeneration and neuronal loss may thus be present in varying degrees. In addition, the patients were analysed at different stages in their progressive disease. Differences in postprocessing of the different MRS data may further confuse interpretation of the results.

In conclusion, the phenotype of the patients from this second family with SPG2 caused by the rumpshaker mutation corresponds to the mildest phenotype reported. These data suggest the pathology to be an underlying mild, central, dysmyelinating disorder in combination with a central axonal degeneration

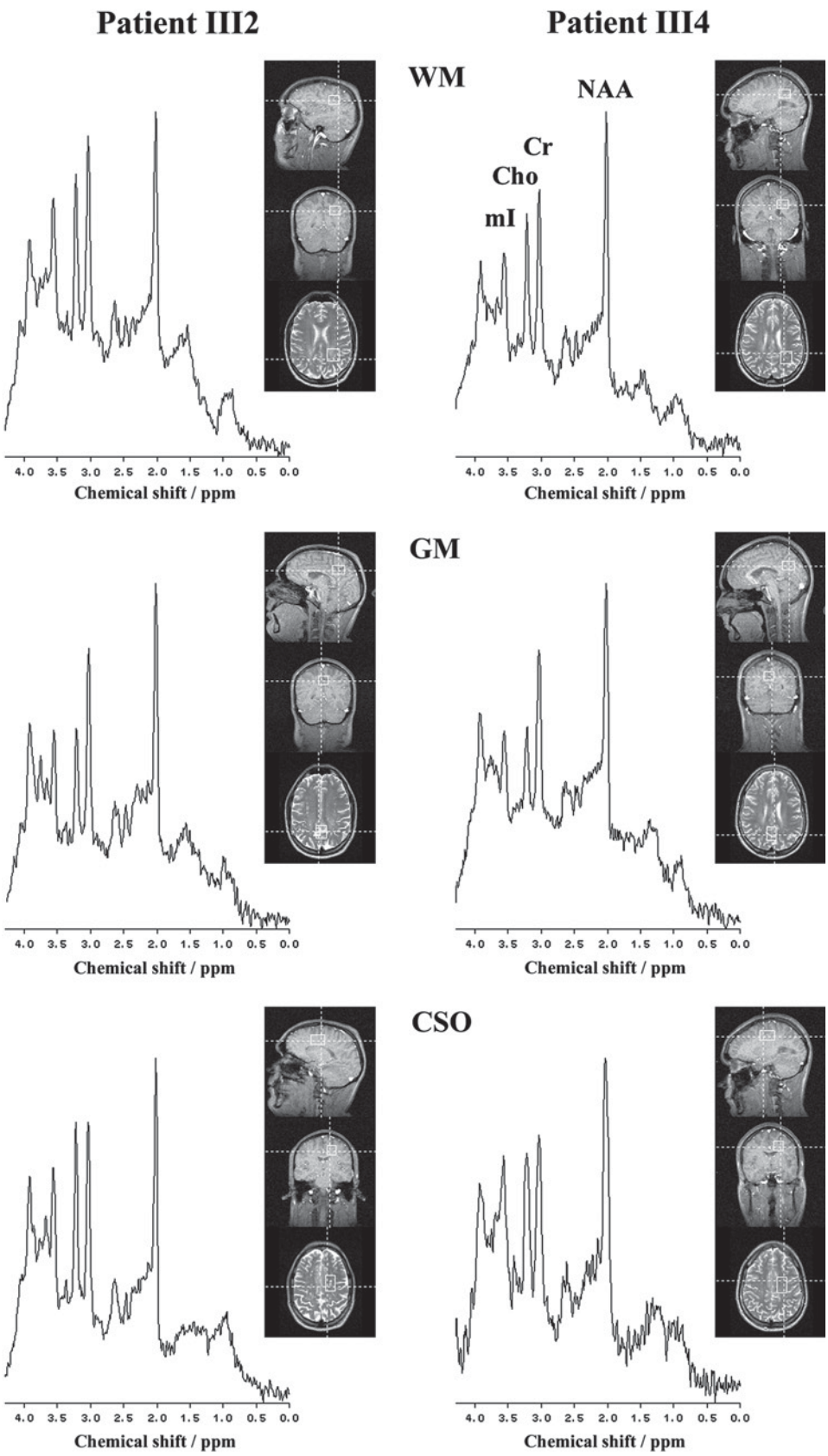

Figure 3 MR spectroscopies. T2 weighted MRI and MRS occipito-parietal primarily white matter (WM), mid-occipital primarily grey matter (GM), centrum semiovale (CSO) in patients III2 and III4.

evolving as a consequence of disease duration as indicated in the oldest patient (III2) by MRS.

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Competing interests None.

Ethics approval Ethics approval was provided by the Copenhagen Ethics commitee.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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