PLP1 mutations and central demyelination

Evidence from electrophysiologic phenotyping in female manifesting carriers

Michael J. Keogh, MRCP; Stephan R. Jaiser, PhD, MRCP; Hannah E. Steele, MRCP; Rita Horvath, MD, PhD; Patrick F. Chinnery, PhD, FRCP, FMedSci; Mark R. Baker, PhD, MRCP

The clinical scenario of a woman aged 30–50 years presenting with progressive lower limb spasticity, asymmetric changes on visual evoked potentials (VEPs), somatosensory evoked potentials (SEPs), and motor evoked potentials (MEPs) consistent with central demyelination would commonly indicate primary progressive multiple sclerosis (PPMS).

We describe 2 cases in which neurophysiologic investigations showed these changes, but genetic testing confirmed both cases to carry mutations in *PLP1*, consistent with a diagnosis of spastic paraplegia type 2. This widens the phenotype of hereditary spastic paraplegia (HSP), providing insight into both the diagnostic challenges and pathophysiology of *PLP1* disease.

Cases

Patient 1 A 32-year-old woman presented with a 4-year history of progressive lower limb stiffness. She remained independently mobile and could walk a mile without assistance. Examination revealed normal higher mental function and cranial nerves. Upper limb reflexes were brisk, but tone, power, and sensation were normal. There was a marked spastic paraparesis, with extensor plantars but no sensory component or ataxia. MRI scans of brain and spine at age 33 were normal (figure, A–D).

Two of the patient's brothers had been diagnosed in infancy with Pelizaeus-Merzbacher (PM) disease due to a deletion of exon 5–7 of *PLP1* using a multiplex ligation-dependent probe amplification. Carrier status was confirmed in the mother (currently asymptomatic at age 58) and the patient.

Patient 2 A 47-year-old woman presented with 2 years of stiffening gait and increased urinary frequency. Cranial nerves and upper limb sensorimotor examination were normal. Lower limb tone was increased, with brisk knee jerks but absent ankle jerks. Plantars were flexor and gait was spastic. MRI was normal at presentation and again 11 years later (figure, E–H). At age 58, she is nonambulatory with a severe spastic paraparesis.

Four of her sons had been diagnosed in infancy with PM due to a hemizygous frameshift mutation (c.49_52delGCTT, p. Ala17Profs*29) in exon 2 of *PLP1*, subsequently also confirmed in the patient. There was no antecedent history of neurologic disease, with both parents living into their 70s.

Practical Implications

PLP1 mutations should not be overlooked in cases of possible spinal primary progressive multiple sclerosis.

Wellcome Centre for Mitochondrial Research, Institute of Genetic Medicine, Centre for Life (MJK, HES, RH, PFC), and Institute of Neuroscience (SRJ, MRB), Newcastle University; Departments of Neurology (MJK, SRJ, HES, RH, PFC, MRB) and Neurophysiology (SRJ, MRB), Royal Victoria Infirmary, Newcastle Upon Tyne; and Department of Clinical Neurosciences (MJK, PFC), University Neurology Unit, Cambridge Biomedical Campus, UK.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Correspondence to: mjk72@cam.ac.uk

Figure MRI and neurophysiologic investigation results from patients 1 and 2

(A-D) Fluid-attenuated inversion recovery (FLAIR) and T2 MRI of patient 1. (E-H). FLAIR and T2 MRI of patient 2. (I, J) Clinical pedigrees of patients 1 and 2, respectively. (K-M) Examples of motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) recorded from patient 1. For all neurophysiologic investigations, gray boxes show the normal range (mean +2 SD). Upper limb MEPs were delayed on the left and normal on the right (not shown); lower limb MEPs were reduced in amplitude and significantly delayed (MEPs from healthy age-matched control plotted for comparison in gray). The MEP time base was adjusted for peripheral motor conduction time and therefore reflects central motor conduction time only. Lower limb SEPs were absent on the left and delayed on the right (maroon: left; gray: right; upper limit of normal 50 ms, representing mean P1 latency +2 SD derived from a local control dataset). Note that such patchy/asymmetric MEP and SEP findings are atypical for HSP; in HSP, MEP abnormalities are limited to the lower limbs, where symmetrically delayed CMCTs are the most common observation (for discussion, see supplemental data in Baker et al.⁹). ADM = abductor digiti minimi; EDB = extensor digitorum brevis; FDS = flexor digitorum superficialis; TA = tibialis anterior.

Neurophysiologic investigations

The results of neurophysiologic tests are summarized in table e-1 at Neurology.org/cp.

Patient 1 At age 33, MEPs were well-formed but unilaterally delayed in the upper limbs and poorly formed in the lower limbs, consistent with corticospinal tract demyelination (figure, K–L). Pattern VEPs showed significant asymmetry (table e-1). Somatosensory evoked potentials showed significant slowing in the upper limbs and borderline prolongation of the P1 component of the right lower limb. The left lower limb SEP was absent (figure, M).

Patient 2 At age 58, patient 2 had normal NCS. MEPs showed poorly formed patchy and asymmetric central motor conduction delays consistent with cervical corticospinal tract demyelination. Lower limb SEPs were significantly delayed bilaterally consistent with demyelination within the central somatosensory pathways. SEPs performed 12 years earlier were normal (data not shown).

DISCUSSION

Mutations in proteolipid protein 1 (*PLP1*) cause a wide clinical and radiologic spectrum of disease in males.¹ Cases of female manifesting carriers are extremely rare, but our study highlights that such cases can present with pure HSP without major neuroradiologic abnormalities. This is in contrast to manifesting carrier females with large copy number variations, who may have a more severe phenotype and an early onset leukodystrophy,² but similar to those with partial deletions, who exhibit only minimal hypomyelination.³ Taken together, these findings may begin to suggest a potential genotype–phenotype correlation in manifesting carriers, though further data are required.

Both cases presented here closely resembled PPMS particularly given the evidence of dissemination in space (patient 1) and time on evoked potential studies (patient 2).⁴ The neurophysiologic findings are also incongruous with classical HSP disorders in which upper limb abnormalities and asymmetric lower limb changes are atypical (for discussion, see supplemental data in Baker et al.⁵). Without affected male offspring or siblings, a genetic etiology would likely not have been considered in our cases. With increasing nulliparity and single-child families within Western societies, these cases highlight that clinicians should remain vigilant for X-linked forms of disease, such as *PLP1* mutations in PPMS, even in what may clinically and neurophysiologically resemble ostensibly sporadic disorders.⁶

Finally, the mechanism by which *PLP1* mutations may cause asymmetric and tract-specific demyelination is highly intriguing. Skewed inactivation of the X chromosome within the germline can modify the phenotype, perhaps explaining the phenotypic discordance between both patients and their mothers in our study.⁷ However, the important asymmetric and tract-specific neurophysiologic findings in our cases suggest that somatic X-linked inactivation within the CNS may also modulate the phenotype.

REFERENCES

1. Hobson GM, Kamholz J. PLP1-Related disorders. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews. Seattle: University of Washington; 2013.
2. Carvalho CM, Bartnik M, Pehlivan D, Fang P, Shen J, Lupski JR. Evidence for disease penetrance relating to CNV size: Pelizaeus-Merzbacher disease and manifesting carriers with a familial 11 Mb duplication at Xq22. *Clin Genet* 2012;81:532–541.
3. Matsufuji M, Osaka H, Gotoh L, Shimbo H, Takashima S, Inoue K. Partial PLP1 deletion causing X-linked dominant spastic paraplegia type 2. *Pediatr Neurol* 2013;49:477–481.
4. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
5. Baker MR, Fisher KM, Whittaker RG, Griffiths PG, Yu-Wai-Man P, Chinnery PF. Subclinical multisystem neurologic disease in “pure” OPA1 autosomal dominant optic atrophy. *Neurology* 2011;77:1309–1312.
6. Warshawsky I, Rudick RA, Staugaitis SM, Natowicz MR. Primary progressive multiple sclerosis as a phenotype of a PLP1 gene mutation. *Ann Neurol* 2005;58:470–473.

Supplemental Data

Neurology.org/cp

7. Woodward K, Kirtland K, Dlouhy S, et al. X inactivation phenotype in carriers of Pelizaeus-Merzbacher disease: skewed in carriers of a duplication and random in carriers of point mutations. *Eur J Hum Genet* 2000;8:449–454.

Received November 21, 2016. Accepted in final form January 30, 2017.

AUTHOR CONTRIBUTIONS

M.J. Keogh: study concept and design, analysis and interpretation of data, acquisition of data, drafting/ revising the manuscript. S.R. Jaiser: acquisition of data, analysis and interpretation of data, drafting/ revising the manuscript. H. Steele: acquisition of data, drafting/ revising the manuscript. R. Horvath: study concept and design, drafting/ devising the manuscript. P.F. Chinnery: study concept and design, analysis and interpretation of data, study supervision, drafting the manuscript. M.R. Baker: analysis and interpretation of data, acquisition of data, study supervision, revising/ drafting the manuscript.

STUDY FUNDING

Dr. Keogh is a Wellcome Trust Clinical Research Training Fellow (103396/Z/13/Z). Professor Horvath is a Wellcome Trust Investigator (109915/Z/15/Z), who receives support from the Medical Research Council (UK) (MR/N025431/1), the European Research Council (309548), the Wellcome Trust Pathfinder Scheme (201064/Z/16/Z), and the Newton Fund (UK/Turkey, MR/N027302/1). Professor Chinnery is a Wellcome Trust Senior Fellow in Clinical Science (101876/Z/13/Z) and a UK NIHR Senior Investigator, who receives support from the Medical Research Council Mitochondrial Biology Unit (MC_UP_1501/2) and the Wellcome Trust Centre for Mitochondrial Research (096919Z/11/Z). He receives funding from the Medical Research Council and the National Institute for Health Research Biomedical Research Centre for Ageing and Age-Related Disease award to the Newcastle upon Tyne Hospitals National Health Service Foundation Trust. Dr. Baker is a consultant neurologist and consultant clinical neurophysiologist employed by Newcastle upon Tyne Hospitals NHS Foundation Trust and an honorary senior clinical lecturer at the Institute of Neuroscience. His research laboratories are funded by grants from the NIHR, MRC, and Ataxia UK.

DISCLOSURES

M.J. Keogh and S.R. Jaiser report no disclosures. H. Steele receives salary support from GSK. R. Horvath reports no disclosures. P.F. Chinnery serves as an Associate Editor for *Brain* and receives research support from Medical Research Council (UK), NIHR (England), and Wellcome Trust. M.R. Baker receives research support from NIHR and MRC. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

What Do You Think?

Discover what your colleagues in clinical practice are talking about. And then add to the discussion!

Neurology® Clinical Practice welcomes your feedback on our articles and seeks your practical, real-world experience on how you face opportunities and challenges in clinical practice. Correspondence regarding articles that appear in *Neurology: Clinical Practice* may be sent via e-mail to NCPjournal@neurology.org or by clicking on the “Respond” button in the right column of a full text version of an article.