Rostral and caudal propagation of the myoclonic jerks. The first muscle activated is always the biceps muscle. Caudally it is followed by the m. flexor carpi radialis (FCR), m. rectus femoris, and m. tibialis anterior, respectively. Cranially it is followed by the m. trapezius and m. sternocleidomastoideus (S.C.), while the masseter muscle remained silent.

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SUBCLINICAL MULTISYSTEM NEUROLOGIC DISEASE IN “PURE” *OPA1* AUTOSOMAL DOMINANT OPTIC ATROPHY

Mutations affecting the nuclear gene encoding the mitochondrial *OPA1* protein are the commonest causes of autosomal dominant optic atrophy (DOA). More recently *OPA1* mutations have been shown to cause a disorder of mitochondrial DNA (mtDNA) maintenance, thus explaining the extraocular features observed in ~20% of *OPA1* mutation carriers with “DOA+,” which include deafness, progressive external ophthalmoplegia (PEO), myopathy, ataxia, neuropathy, and spastic paraplegia.^{1,2} However, it remains puzzling why, unlike other hereditary mtDNA maintenance disorders (e.g., *POLG1*),

most *OPA1* mutation carriers only appear to develop isolated optic neuropathy. To determine whether this is actually the case, we looked for electrophysiologic evidence of subclinical multisystem disease in a sample of patients with clinically “pure” DOA. Because spasticity is an unusual clinical finding in mitochondrial disease, we were particularly interested to look for evidence of subclinical corticospinal tract (CST) disease in this clinically asymptomatic group, specifically to gain insight into the role of mitochondrial dysfunction in other more common neurodegenerative motor disorders.

Methods. Fourteen patients with confirmed pathogenic *OPA1* mutations were recruited prospectively: 1) 13 patients with bilateral optic atro-

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phy and no evidence of any neurologic deficit, classified as “pure” DOA; and 2) 1 visually asymptomatic *OPA1* mutation carrier (c.1294A>G) with no clinical or electrophysiologic evidence of optic nerve dysfunction. MRI was performed as part of the patients’ initial diagnostic workup for their unexplained bilateral optic neuropathy. All patients had nerve conduction studies (NCS), needle EMG, and transcranial magnetic stimulation (TMS) was used to obtain motor evoked potentials (MEPs) and test short-interval intracortical inhibition (SICI). Sensory evoked potentials (SEPs) were tested in 5 patients (e-Methods on the *Neurology*[®] Web site at www.neurology.org). This

study had the relevant institutional ethical approval and complied with the Declaration of Helsinki.

Results. Of the “pure” DOA patients, 10/13 (77%) had subclinical electrophysiologic abnormalities (summarized in table e-1) indicative of 1) sensory axonal neuropathy/dorsal root ganglionopathy (DRGopathy) (n = 3); 2) myelopathy (n = 4) with abnormal MEPs only (n = 2), delayed SEPs (n = 1) only, or both (n = 1); or 3) absent SICI (n = 6). The 2 patients (OA-2 and OA-6) with abnormal MEPs had significantly prolonged CMCTs (figure 1), but with normal MEP thresholds and waveforms. In the

Figure 1 Motor evoked potentials (MEPs) and central motor conduction times (CMCTs)

(A, B) Examples of motor evoked potentials (MEPs) obtained from a patient OA-2 (black trace) with subclinical evidence of abnormal central conduction (central conduction delay) and a representative age-matched control (red trace) matched for height and peripheral motor conduction time (PMCT). (A) Upper limb MEPs recorded from right first dorsal interosseous (FDI). (B) Lower limb MEPs recorded from right extensor digitorum brevis (EDB). MEPs are aligned to the stimulus. Each trace is an average of 20 individual MEPs. Dashed vertical lines indicate MEP onsets. (C, D) Summary MEP data for dominant optic atrophy (DOA) and non-DOA patients (n = 14). Central motor conduction times (CMCTs) are plotted against age and compared with normative data. Each data point represents one patient. Solid horizontal lines show the mean CMCT within the normal population and gray boxes extend 2 standard deviations above and below the mean. (C) Upper limb (FDI) CMCTs. (D) Lower limb (EDB) CMCTs.

patient (OA-7) who only had lower limb SEP abnormalities, SEPs were asymmetrically prolonged. One patient (OA-10) had abnormal SEPs, MEPs, and significantly reduced SICI (figure e-2). In 3 patients, absent SICI was the only abnormality found. The *OPA1* mutation carrier (OA-14) nonpenetrant for optic atrophy had definite electrophysiologic evidence of a sensory axonal neuropathy/DRGopathy. No patient had evidence of demyelination or structural abnormalities on MRI.

Discussion. Only ~20% of *OPA1* mutation carriers develop clinically overt extraocular complications in later life.¹ However, our detailed neurophysiologic assessment indicates that multisystem involvement in *OPA1* mutation-associated disease is the norm rather than the exception, consistent with the ubiquitous expression of the *OPA1* protein and its crucial importance to mitochondrial function.⁴ Missense *OPA1* GTPase mutations carry a 3-fold increased risk of developing DOA+, for which a dominant-negative mutational effect has been postulated.^{5,1} Except for one individual (OA-14), the patients included in this study harbored *OPA1* mutations predicted to result in haploinsufficiency, providing a plausible explanation for the milder neurophysiologic findings. Moreover, the 3 patients with normal neurophysiology were younger (mean age 38 years) compared with the rest of the cohort (mean age 52 years), suggesting that, as with clinically overt extraocular disease,¹ the risk of developing subclinical multisystem disease is also age-dependent. In support of this hypothesis, among sibling pairs (table e-1), electrophysiologic abnormalities were milder or absent for the younger family member. The reasons for the early selective vulnerability of retinal ganglion cells and the factors influencing progression to clinically detectable multisystem disease, however, remain to be determined.

Spasticity, the most obvious clinical manifestation of CST disease, is a rare finding in mitochondrial disease. In our cohort, nearly 1 in 4 had prolonged CMCTs, suggesting that CST involvement is more common in mitochondrial disease than previously thought, but presumably masked clinically by the presence of coexistent peripheral neuropathy in other patients.

Among our cohort of “pure” DOA patients, 4/13 (31%) had asymptotically prolonged central conduction times, which fell within the range typical of demyelination.⁶ Although degenerative loss of fast conducting axons could explain these findings, demyelination is a possible alternative explanation, particularly given the fact that oligodendrocyte survival

is critically dependent upon normal mitochondrial function,^{7,4} and central demyelination has been described previously in mitochondrial disease. For example, demyelination within the optic nerve is not only a prominent feature of DOA, but also of Leber hereditary optic neuropathy and Harding disease.⁴ It will therefore be interesting to screen for *OPA1* genetic variants in sporadic central demyelinating disorders such as MS.

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Author contributions: Dr. Mark Baker designed the study, analyzed and interpreted the data, and drafted the manuscript. He also supervised the study, obtained funding for the study, and was responsible for data acquisition and statistical analysis. Karen Fisher designed part of the study, analyzed some of the data, drafted parts of the manuscript, and reviewed and revised the draft manuscript. She also coordinated the study and acquired data. Dr. Roger Whittaker was responsible for some of the data acquisition and interpretation and revised the manuscript. Dr. Philip Griffiths was responsible for the concept and design of the study and contributed patients to the study. Dr. Patrick Yu-Wai-Man was responsible for the concept and design of the study, coordinated the study, interpreted the data, and revised the manuscript. Professor Patrick Chinnery was responsible for the concept and design of the study. He also supervised the study, interpreted the data, and revised the final manuscript.

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

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U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.