

Dorien Weckhuysen, MD
Maarten Schrooten, MD
Philippe Demaerel, MD
Christine Van

Broeckhoven, PhD
Thomas Tousseyn, MD,
PhD
Gabor G. Kovacs, MD,
PhD
Philip Van Damme, MD,
PhD

*Neurol Neuroimmunol
Neuroinflamm*
2015;2:e173; doi: 10.1212/
NXL.0000000000000173

GENETIC CREUTZFELDT-JAKOB DISEASE MIMICKING CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

OPEN

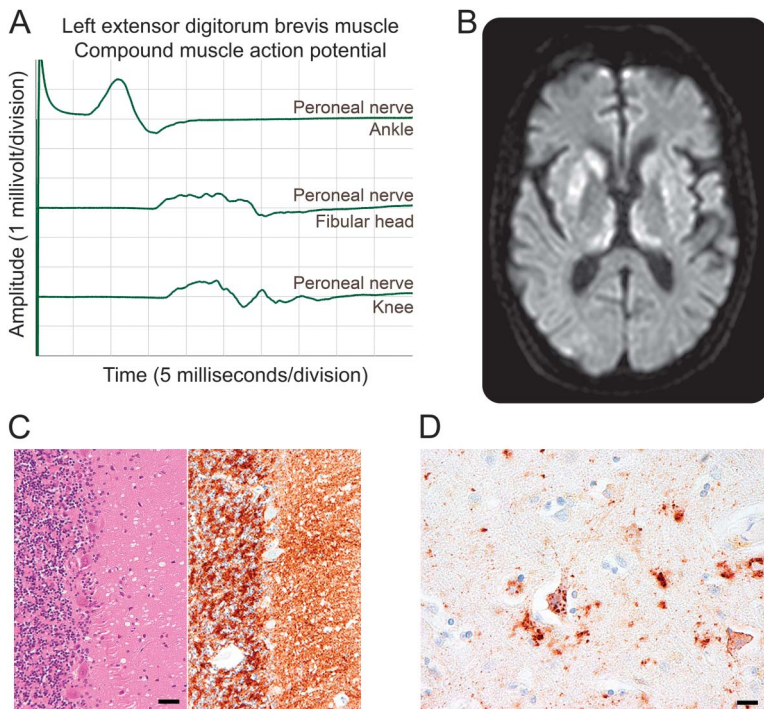
Creutzfeldt-Jakob disease (CJD) is a relentlessly progressive neurodegenerative disorder, belonging to the transmissible spongiform encephalopathies. It is characterized by the deposition of the abnormal isoform of the prion protein (PrP^{sc}), causing spongiform neurodegeneration. The disease is classically known to mainly affect the gray matter of the CNS. However, involvement of the peripheral nervous system (PNS) has been described.^{1–3} Herein, we describe a patient with genetic CJD, in whom the disease presentation was a demyelinating neuropathy reminiscent of chronic inflammatory demyelinating polyneuropathy (CIDP).

Case report. A 55-year-old man with a history of psoriasis was seen at our center because of progressive numbness and paresthesias in his feet, accompanied by gait difficulties since 2 months. A few weeks earlier, he was diagnosed and treated for a suspected Guillain-Barré syndrome in another hospital. He was referred to our center because of disease progression, despite an initial favorable response to IV immunoglobulins. On neurologic examination, evidence of a sensory ataxic neuropathy with distal sensory deficits, diminished deep tendon reflexes in the lower limbs, sensory ataxia, and an unsteady gait were found. Nerve conduction studies confirmed the presence of an inhomogeneous demyelinating neuropathy, with conduction blocks, temporal dispersion, prolonged terminal latencies, reduced conduction velocities, and prolonged F-wave latencies, and were therefore suggestive of a diagnosis of CIDP (figure, A). He fulfilled the European Federation of Neurological Societies criteria of definite CIDP. On lumbar puncture, we found an albuminocytologic dissociation (albumin 1,830 mg/L; normal range 139–246 mg/L). Infectious and paraneoplastic causes were excluded. Anti-GM2 antibodies (titer 1/2,000) were present. We administered further treatment with IV immunoglobulins every 6 weeks, but no significant response to this treatment was observed. Therefore, a trial with oral corticosteroids was initiated. However, his condition

quickly worsened, and 8 months after the initial CIDP-like presentation, he clearly developed cognitive problems, together with a further worsening of the gait difficulties. Mini-Mental State Examination score was 23/30, cerebellar ataxia in the limbs was noted together with hyperreflexia in the upper limbs and increased muscle tone in the 4 limbs. In the following month, Mini-Mental State Examination score decreased to 18/30, after which the patient became bedridden and apathic. Consecutive MRI of the brain showed bilateral diffusion-weighted and fluid-attenuated inversion recovery imaging hyperintensities in the medial thalamus and basal ganglia (figure, B).⁴ Several EEGs showed diffuse slowing, but no periodic discharges were found. Protein 14-3-3 in CSF was negative, but total tau levels were clearly elevated (>1,200 pg/mL, upper limit of normal 367 pg/mL). The patient died of pneumonia 11 months after the onset of symptoms. In the neocortical and subcortical regions, we observed various degrees of spongiform change (figure, C). Immunostaining for PrP (antibody 12F10) revealed prominent synaptic (figure, C) and perineuronal immunoreactivity for the disease-associated PrP. In addition, peculiar intraneuronal globular immunoreactivity (figure, D) was observed in the deeper layers of the neocortex and in the brainstem neurons; this immunomorphology was strongly suggestive of a genetic etiology. Indeed, genetic analysis revealed a p.Glu200Lys mutation in the *PRNP* gene on chromosome 20, which is a frequently found pathogenic mutation in patients with CJD. Unfortunately, no peripheral nerve tissue was available for examination.

Discussion. Our findings support the notion that CJD can present as a subacute demyelinating neuropathy and underscores the idea that PNS involvement is an integral part of CJD in a subset of patients. Although a manifest axonal or demyelinating peripheral neuropathy is rare in CJD (up to 15% of E200K genetic CJD cases),^{2,3,5–7} subclinical PNS involvement can be documented using nerve conduction studies in patients with sporadic CJD.¹ Axonal sensorimotor polyneuropathy and CIDP-like neuropathy have been described as presenting

Figure Chronic inflammatory demyelinating polyneuropathy-like picture in patient with proven Creutzfeldt-Jakob disease



(A) Example of partial conduction block/temporal dispersion in left peroneal nerve upon nerve conduction studies, 2 months after disease onset. (B) Diffusion-weighted image of the brain showing hyperintensities in the medial thalamus and basal ganglia. (C) Hematoxylin & eosin staining (left side of image) of the cerebellar cortex with spongiform change in the molecular layer and diffuse synaptic prion protein (PrP) immunoreactivity (right side of image). (D) PrP immunoreactive aggregates in the neuropil and in neurons in the deeper layers of the frontal cortex. Bar in panel C represents 30 μm , and the bar in D represents 10 μm .

symptoms in cases with sporadic CJD.^{2,5} We expand these findings by reporting a genetic CJD presenting with a CIDP-like phenotype 8 months before overt CNS involvement. This suggests that Schwann cells and peripheral nerve cells are also vulnerable to prion-induced damage.

CJD should be considered as rare CIDP mimic in patients with fast disease progression and lack of response to immunotherapy and particularly if additional symptoms suggesting CNS involvement appear.

From the Departments of Neurology (D.W., M.S., P.V.D.), Radiology (P.D.), and Pathology (T.T.), University Hospitals Leuven; KU Leuven (M.S.), University of Leuven, Department of Neurosciences, Experimental Neurology, Laboratory for Cognitive Neurology, Leuven; Neurodegenerative Brain Diseases Group (C.V.B.), Department of Molecular Genetics, VIB, Antwerp; Laboratory of Neurogenetics (C.V.B.), Institute Born-Bunge, University of Antwerp, Belgium; Institute of Neurology (G.G.K.), Medical University of Vienna, Austria; KU Leuven (P.V.D.), University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease, Leuven; and VIB (P.V.D.), Vesalius Research Center, Laboratory of Neurobiology, Leuven, Belgium.

Author contributions: Dr. Weckhuysen: acquisition of data, analysis and interpretation, writing of the manuscript. Dr. Schrooten: acquisition of data, critical revision of the manuscript. Dr. Demaerel:

acquisition of data, critical revision of the manuscript. Dr. Van Broeckhoven: acquisition of data, critical revision of the manuscript. Dr. Tousseyn: acquisition of data, critical revision of the manuscript. Dr. Kovacs: acquisition of data, analysis and interpretation, critical revision of the manuscript. Dr. Van Damme: study concept and design, analysis and interpretation, study supervision, critical revision of the manuscript.

Acknowledgment: This study is supported by a grant from the KU Leuven (GOA/11/014) and by the Interuniversity Attraction Poles (IUAP) program P7/16 of the Belgian Federal Science Policy Office. P.V.D. holds a senior clinical investigatorship from the Flemish Fund for Scientific Research (FWO-Vlaanderen) and is supported by the Belgian ALS league.

Study funding: This study is supported by a grant from the KU Leuven (GOA/11/014) and by the Interuniversity Attraction Poles (IUAP) program P7/16 of the Belgian Federal Science Policy Office.

Disclosure: D. Weckhuysen and M. Schrooten report no disclosures. P. Demaerel is a section editor for Neuroradiology. C. Van Broeckhoven is an associate editor for Genes, Brain and Behavior, Neuro-Molecular Medicine, and NEJM, is communicating editor for Human Mutation Member, received research support from VIB and Competitive Research Funding. T. Tousseyn reports no disclosures. G.G. Kovacs is on the scientific advisory board for Gedeon Richter Pl., received speaker honoraria from Novartis, is on the editorial board for Acta Neuropathologica and Neuropathology and Applied Neurobiology, is on the executive advisory board for Clinical Neuropathology, holds a patent for anti-alpha-synuclein antibody 5G4, received publishing royalties from Cambridge University Press, and received research support from Federal Ministry of Health, Austria; Austrian Reference Centre for Human Prion Disease, FP7 EU Project Develage. P. Van Damme served on the scientific advisory board for Biogen, received research support from FWO-Vlaanderen. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received June 22, 2015. Accepted in final form September 23, 2015.

Correspondence to Dr. Van Damme: philip.vandamme@uzleuven.be

1. Niewiadomska M, Kulczycki J, Wochnik-Dyjas D, et al. Impairment of the peripheral nervous system in Creutzfeldt-Jakob disease. *Arch Neurol* 2002;59:1430–1436.
2. Kovacs T, Aranyi Z, Szirmai I, Lantos PL. Creutzfeldt-Jakob disease with amyotrophy and demyelinating polyneuropathy. *Arch Neurol* 2002;59:1811–1814.
3. Esiri MM, Gordon WI, Collinge J, Patten JS. Peripheral neuropathy in Creutzfeldt-Jakob disease. *Neurology* 1997; 48:784.
4. Demaerel P, Baert AL, Vanopdenbosch L, Robberecht W, Dom R. Diffusion-weighted magnetic resonance imaging in Creutzfeldt-Jakob disease. *Lancet* 1997;349:847–848.
5. Zephir H, Stojkovic T, de Seze J, et al. Severe and rapidly evolving peripheral neuropathy revealing sporadic Creutzfeldt-Jakob disease. *J Neurol* 2009;256:134–136.
6. Antoine JC, Laplanche JL, Mosnier JF, Beaudry P, Chatelain J, Michel D. Demyelinating peripheral neuropathy with Creutzfeldt-Jakob disease and mutation at codon 200 of the prion protein gene. *Neurology* 1996; 46:1123–1127.
7. Kovacs GG, Seguin J, Quadrio I, et al. Genetic Creutzfeldt-Jakob disease associated with the E200K mutation: characterization of a complex proteinopathy. *Acta Neuropathol* 2011;121:39–57.