Clinical commentary

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Presentation of an unusual patient with Lafora disease

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ABSTRACT – Lafora disease is a rare, fatal, autosomal recessive progressive myoclonic epilepsy. The condition is characterised by seizures, myoclonus and dementia. In this case report, a patient who presented with generalised tonic-clonic seizures at the age of 30 is discussed. Until the age of 48, the patient did not have myoclonic jerks or ataxia clinically, but had well controlled seizures. He developed dementia and late extrapyramidal signs. Axillary skin biopsy revealed typical Lafora inclusion bodies. Genetic analysis showed a mutation in the *EMP2B* gene. To our knowledge, this is the first description of a patient suffering from a Lafora disease without disabling myoclonus and ataxia but rather rare seizures, extrapyramidal signs, and dementia.

Key words: late onset dementia, extrapyramidal signs, epilepsy, disabling myoclonus

Lafora disease (LD) phenomenologically belongs to the spectrum of progressive myoclonic epilepsy (PME) and generally presents a more or less homogeneous phenotype, characterised by seizures preceding visual auras, myoclonus, dementia, and ataxia (Minassian, 2002). Some recent studies and case reports have reported variability of the clinical characteristics with respect to the age at onset and prognosis (Minassian, 2002; Baykan *et al*., 2005; Ganesh *et al*., 2002). This case report describes a male patient at the age of 30 presenting with rare generalised tonic-clonic jerks, dementia at the age of 30, and late-onset extrapyramidal signs, but no disabling myoclonus or ataxia. Axillary skin biopsy and genetic analysis confirmed the diagnosis of LD.

Case report

In October 1998, a 35-year-old male patient was referred to our epilepsy centre for the evaluation of three generalised tonic-clonic seizures (without aura) and cognitive decline within five years. Examination of his family history revealed first degree consanguinity between his parents. The patient had six siblings. One of his older brothers died as a result of an epileptic disorder which was not classified with regard to syndromes. The onset of epilepsy occurred at the age of 11 years and the patient presented with myoclonic jerks and a progressive course to a bedridden level and finally death within five years. The patient and the observers reported that there was no absence or myoclonus in his past history.

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His neurological examination at admission revealed only mild to moderate cognitive dysfunction and apathia. EEG revealed brief generalised epileptiform activities on a slow background and no increase in photosensitivity (*figure 1*). Retinal examination and routine biochemistry including lactate levels were unremarkable. Cranial MRI and somatosensorial evoked potential recordings were normal. Sodium valproate treatment was started. He had a neuropsychological assessment when he was 37 which revealed severe impairment of memory and frontal lobe functions. Seizures remitted and cognitive dysfunction deteriorated which led to his retirement at the age of 40 years. Mini-mental test score was 10/30. An axillary skin biopsy revealed Lafora inclusion bodies (*figures 2 and 3*). When he was 46, he presented with mild bradykinesia and resting tremor of the left upper limb. In his recent neurological examination (48 years old), he had behavioural problems, dementia and right-sided resting tremor, bilateral asymmetric rigidity, bilateral bradykinesia, hypomimia, mild anteflexion posture, mild Parkinsonian gait, sphinctary dyscontrol and sebaceous skin. He had no seizure recurrences during the follow-up. Valproate treatment was replaced with levetiracetam which did not resolve Parkinsonian symptoms within six months. Electrophysiological tremor analysis revealed a 5.5-Hz alternating resting tremor and 6-6.5-Hz postural tremor. With the arms outstretched, occasional negative and positive myoclonic activity, which was not clinically apparent (*figure 4*), was recorded. High-amplitude C reflex during the stimulation of median nerve below motor threshold was also recorded (*figure 5*). All EEGs during follow-up were similar to the initial EEG.

Mutational scanning of the *EPM2A* and *EPM2B* genes by PCR amplification and subsequent DNA sequence analysis revealed a c.436 G>A homozygous substitution in exon 1 of the *EPM2B* gene which results in the recurrent missense mutation (Asp146Asn) in the malin protein (http://projects.tcag.ca/lafora).

Discussion

Lafora disease is an autosomal recessive PME. Onset is between ages nine and 18 years (Minassian, 2002). The typical features are myoclonic jerks, generalised tonic-clonic seizures with visual auras, ataxia, and dementia. Generalised or segmental, spontaneous and action myocloni associated with EEG paroxysms are prominent features and the presence of negative myoclonus associated with polyspike-wave discharges is typical and common (Reutens *et al*., 1993). Photo-convulsive response on EEG is a hallmark. High-amplitude cortical SEPs (giant SEPs) are also typical (Shibasaki, 2002). Diagnosis depends on axillary skin biopsy and genetic analysis (Minassian, 2002; Ganesh *et al*., 2002; Lesca *et al*., 2010).

In this case description, an atypical LD patient is presented. The severity and onset age of LD are variable; however, to our knowledge, there is no similar case

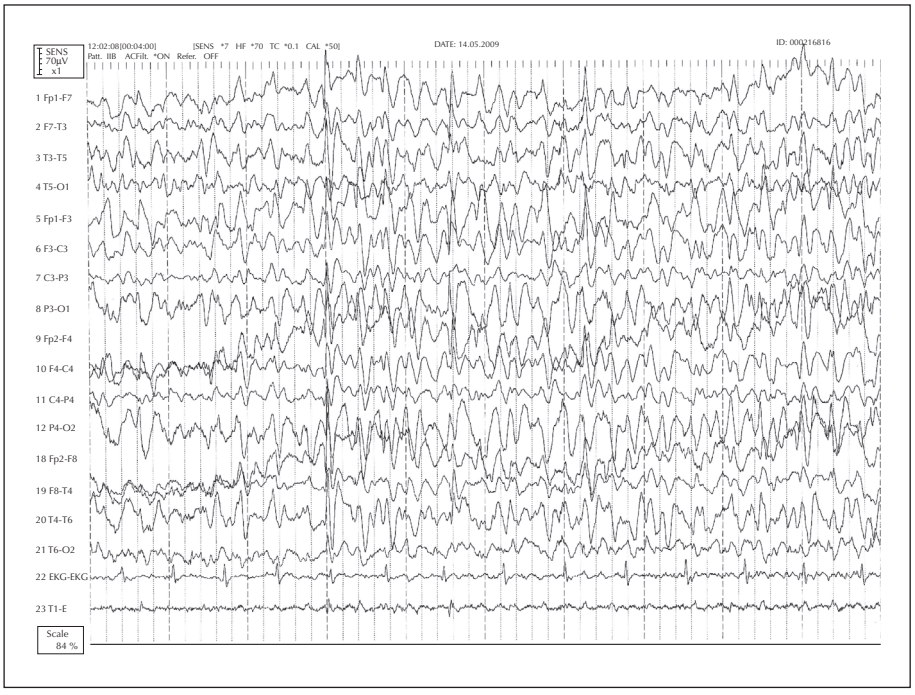

Figure 1. EEG revealed brief generalised epileptiform activities on a slow background.

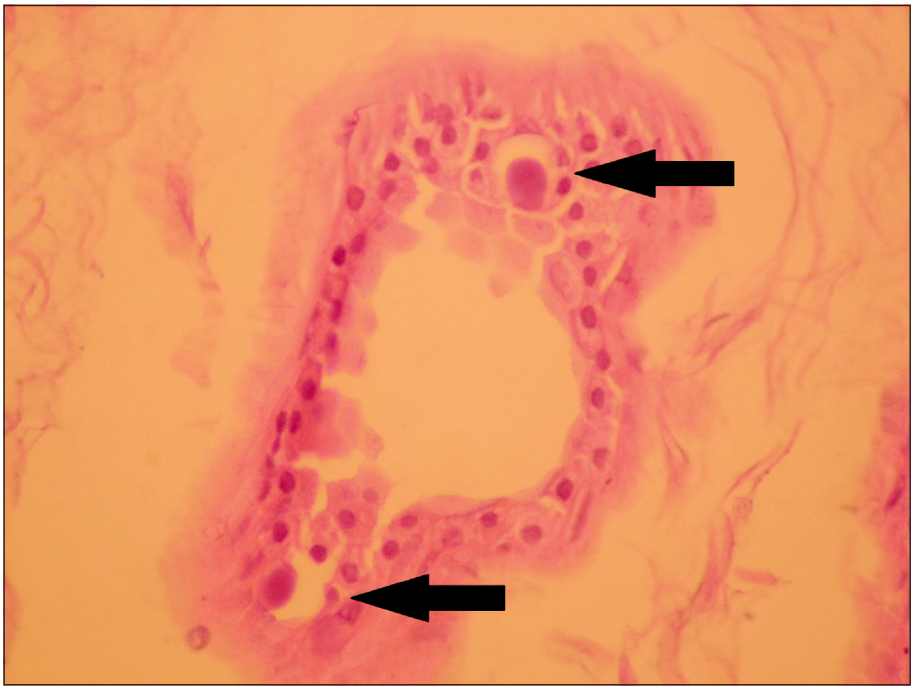

Figure 2. Lafora bodies in axillary biopsy, examined by haematoxylin/eosin staining.

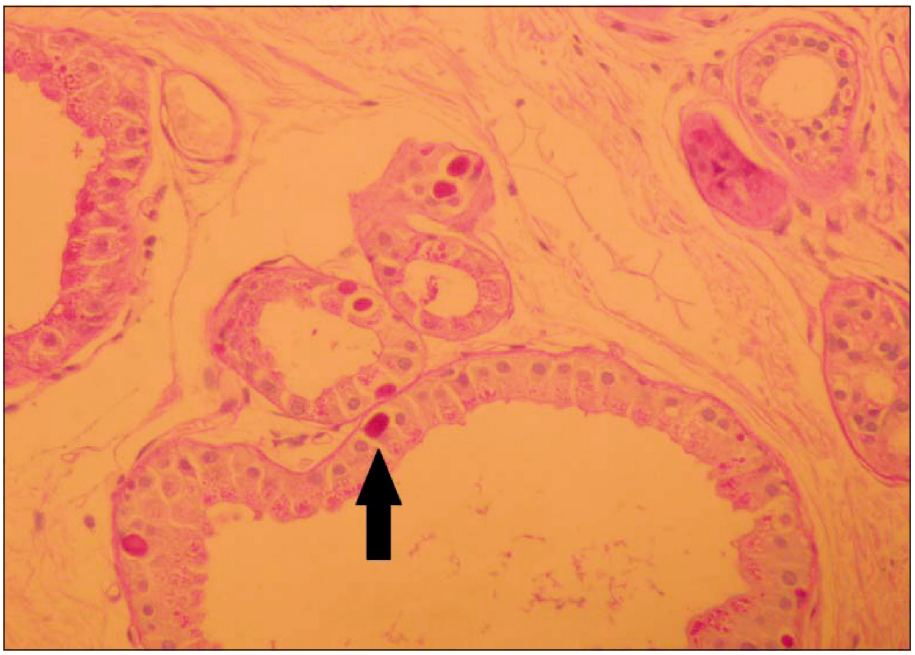

Figure 3. Lafora bodies in axillary biopsy, examined by PAS staining.

description in the literature with rare well-controlled seizures, dementia, and late extrapyramidal signs without disabling myoclonic jerks. This patient presented with a late onset of disease and never experienced disabling myoclonus. Prominent features were dementia, well controlled seizures, and late-onset extrapyramidal signs. As one of his brothers died from a disease resembling PME and since his parents were consanguineous, he was examined in the context of PMEs. Extrapyramidal signs may be the result of chronic valproate use. However, this well-known rare side effect of valproate is reversible and may not exceed six months after withdrawal, according to case descriptions in the literature (Onofrj *et al*., 1998; Ristić *et al*., 2006).

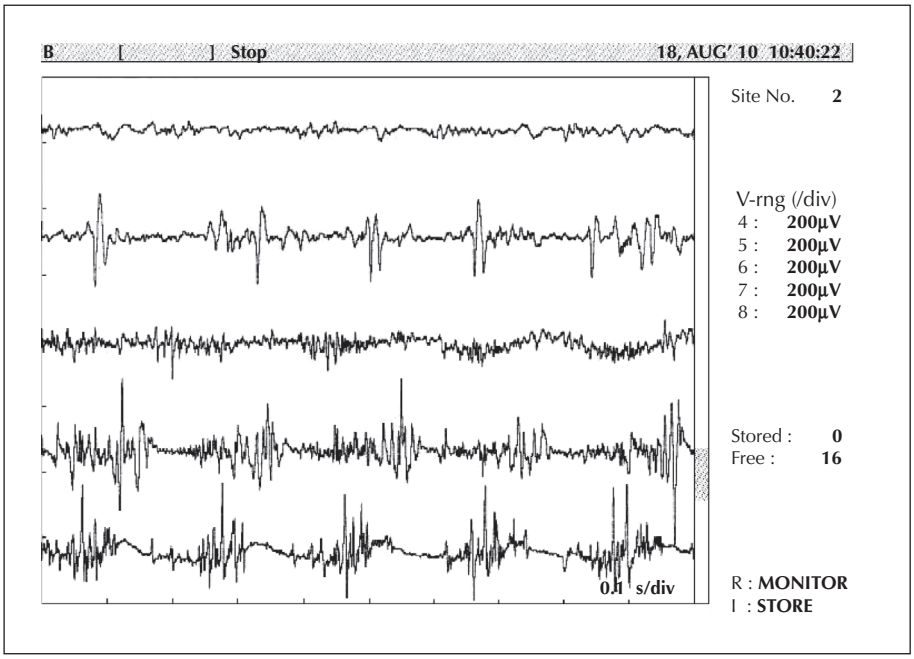

Figure 4. Alternating 5.5-Hz resting tremor resembling Parkinson's disease.
Channels: left deltoid, biceps brachii, flexors of forearm, extensors of forearm, and abductor pollicis brevis.

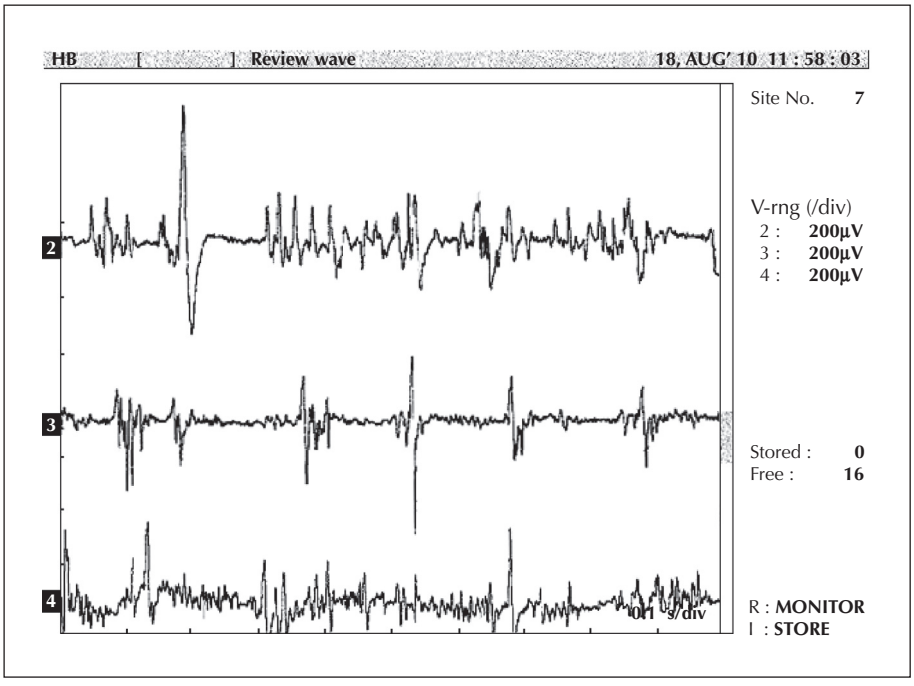

Figure 5. High-amplitude C reflex from biceps and deltoid muscles, elicited with the excitation of median nerve with 8 mA, at the same side.
Channels: right abductor pollicis brevis, left deltoid, biceps brachii, flexors of forearm, extensors of forearm, and left abductor pollicis brevis.

Varying degrees of Lafora body inclusions are observed in all regions of the central nervous system (CNS) including basal ganglia (Minassian, 2001; Striano *et al*., 2009; Kaufman *et al*., 1993). Thus, extrapyramidal signs might not be unexpected, despite a lack of reports. Patients with LD usually die during adolescence which may explain the absence of additional CNS findings. As a progressive disease, sufficient

accumulation of inclusions in basal ganglia to a critical level may delay overt signs.

In a recent review, it was concluded that more careful and extensive description of the clinical phenotype (follow-up) of patients and their mutational genotype could provide better insight into the genotype/phenotype correlation and the existence of possible modifiers for LD. Beyond the clinic, elucidation of the biological functions of the two known genes and identification of at least another, as yet unknown, gene are necessary to better understand the disease mechanism (Singh and Ganesh, 2009). Recently, a protein targeting to glycogen (PTG) variant that contributes to a milder phenotype of Lafora disease has also been reported (Guerrero *et al*., 2011). In summary, we suggest that any progressive disease presenting with epileptic seizures, cognitive decline and late extrapyramidal signs, even without disabling myoclonic jerks, should be investigated for LD. □

Disclosures.
None of the authors has any conflict of interest to disclose.

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