Clinical commentary

Epileptic Disord 2020; 22 (2): 233-6

Early Parkinsonism in a Senegalese girl with Lafora disease

Francesca Ragona [1], Laura Canafoglia [2], Barbara Castellotti [3], Roberta Solazzi [1], Sara Gabbiadini [4], Elena Freri [1], Vidmer Scaioli [2], Jacopo Cosimo DiFrancesco [1,5], Cinzia Gellera [3], Tiziana Granata [1]

[1] Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Member of the ERN EpiCARE, Milano
[2] Neurophysiopathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano
[3] Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano
[4] Unit of Child Neuropsychiatry, Ospedale Papa Giovanni XXIII, Bergamo
[5] Department of Neurology and Epilepsy Center, Milan Center for Neuroscience, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

Received September 24, 2019; Accepted January 11, 2019

ABSTRACT – We report the atypical presentation of Lafora disease in a Senegalese girl carrying the homozygous variant, c.560A>C, in the *NHLRC1* gene. At 13 years, the patient developed myoclonic and visual seizures, progressive psychomotor slowing, and cognitive decline. At 14 years, a neurological examination showed severe hypomimia, bradykinesia, rigidity and low-amplitude myoclonic jerks. Flash-visual and somatosensory evoked potentials showed an increased amplitude of the cortical components, while an electroretinogram showed attenuated responses. An EEG showed diffuse polyspikes associated with positive-negative jerks as well as posterior slow waves and irregular spikes. The electroclinical picture suggested the diagnosis of Lafora disease regarding the association of visual seizures, cognitive deterioration, and action myoclonus, together with the EEG and evoked potential findings. Two uncommon findings were the prominence of extrapyramidal signs in the early stage of disease (which are rarely reported) and attenuation of electroretinal responses. We consider that Lafora disease should be included in the diagnostic work-up for juvenile Parkinsonism, when associated with epilepsy.

Key words: Lafora disease, progressive myoclonus epilepsy, Parkinsonism, *NHLRC1* gene

Correspondence:
Laura Canafoglia
Clinical Neurophysiology and Epilepsy Center,
Fondazione IRCCS Istituto Neurologico "C. Besta,"
Via Celoria 11, 20133 Milan, Italy
<laura.canafoglia@istituto-besta.it>

doi:10.1684/epd.2020.1150

Lafora disease (LD) is a progressive myoclonus epilepsy caused by recessive inherited mutations in the *EPM2A* gene encoding for laforin or *NHLRC1* gene encoding for malin. The disease is characterized by drug-resistant tonic-clonic and visual seizures, spontaneous and multifocal myoclonus, ataxia, dementia and late spasticity (Van Heycop Ten Ham, 1974). Electroencephalogram (EEG) is typically characterized by posterior slowing and diffuse and posterior spike and

waves and multiple spikes, frequently associated with positive and negative jerks. Neurophysiological findings typically include giant somatosensory evoked potentials (SEPs) and giant visually evoked potentials (VEPs) (Canafoglia *et al.*, 2004).
We describe the atypical presentation of LD in a Senegalese girl carrying a rare mutation in the *NHLRC1* gene, which, so far, has only been reported in one family from Mali (Traoré *et al.*, 2009). This report widens the phenotypic spectrum of LD, a rare and probably under-diagnosed condition in sub-Saharan Africa.

Case study

The patient, now aged 15 years, was the first child of healthy consanguineous parents, both from a small village in Senegal. Her psychomotor development was normal and her past medical history uneventful.
At the age of 13 years, the girl started experiencing myoclonic seizures, which progressively increased in frequency, despite treatment with levetiracetam. The clinical picture worsened in the following year regarding the appearance of tonic-clonic seizures, occasionally preceded by visual symptoms (vision of a rainbow-like picture). Treatment with levetiracetam, ethosuximide and clobazam failed to control seizures. Moreover, psychomotor slowing and cognitive decline with ensuing learning difficulties became evident.
At our first evaluation, at the age of 14 years, the neurological examination was characterized by severe hypomimia, bradykinesia, and rigidity, with cogwheel phenomenon. The girl was able to walk unassisted, but the gait was characterized by reduced stride length and walking speed. Subtle and low-amplitude hyperkinesia was detectable during fine motor skills and the Mingazzini test.
The severity of intellectual disability prevented administration of formal neuropsychological tests. Verbal production was virtually absent, and language comprehension impaired. Funduscopy was normal.
The EEG recordings showed diffuse polyspikes associated with positive-negative jerks (*figure 1A, C*), as well as posterior slow waves and irregular spikes, increased by intermittent photic stimulation (*figure 1B, C*). The polymyography showed short sequences of brief synchronous EMG bursts, thus demonstrating that the observed hyperkinesia corresponded to myoclonic jerks (*figure 1F*). Flash-VEPs showed increased P1-N1 (105 μV) and N1-P2 (115 μV) components (*figure 1D, upper part*), whereas electroretinogram (ERG) showed attenuated responses (*figure 1D, lower part*). SEPs showed giant N20-P25 (25 μV) and P25-N33 (55 μV) components (*figure 1E*). Brain MRI was normal.
The clinical picture, characterized by epilepsy with visual-onset seizures, action myoclonus, motor and mental deterioration, together with the neurophysiological findings, pointed to the diagnosis of progressive myoclonus epilepsy. This hypothesis was confirmed by next-generation sequencing (NGS) analysis of a panel containing 188 genes related to epileptic encephalopathies and myoclonus epilepsies. Molecular analysis showed the presence of the homozygous nucleotide substitution c.560A>C in the *NHLRC1* gene, resulting in the missense amino acid substitution p.His187Pro (CM099566 described by Traorè *et al.*, 2009). This mutation is present, in heterozygous form, in both parents. Based on this genetic panel, no other mutation of possibly/probably or clearly pathogenic significance has been detected.

Discussion

In the patient reported here, the association of visual seizures, cognitive deterioration, and action myoclonus, together with the EEG and evoked potential findings were consistent with the diagnosis of LD (Van Heycop Ten Ham, 1974; Franceschetti *et al.*, 2014). We report this case to underscore two uncommon findings: the prominence of extrapyramidal signs, with features of juvenile Parkinsonism, in the early stage of disease, and the attenuation of electroretinal response.
The term "juvenile Parkinsonism" refers to conditions characterized by onset of Parkinsonian symptoms and signs before age 21 years. The aetiology of juvenile Parkinsonism is heterogeneous and includes genetic and acquired causes. The clinical presentation may be that of typical Parkinson disease, with rigidity, tremor and bradykinesia, but often includes atypical features, such as other movement disorders, early cognitive decline, behavioural disturbances, and epileptic seizures (Niemann and Jankovic, 2019).
Parkinsonism may appear during the course of LD, but has been reported as a key or early symptom in only few patients with LD due to *EPM2A* or *NHLRC1* mutations (Gökdemir *et al.*, 2012; Hajnsek *et al.*, 2013; Linch *et al.*, 2016; Yildiz *et al.*, 2017). In particular, the presence of Parkinsonism has been well described in a teenager who experienced difficulty in repetitive movements and resting tremor as the initial symptoms of the disease, followed by bradykinesia and rigidity in the following months (Yildiz *et al.*, 2017). Our case report, together with the few cases previously described, suggests that LD should be considered in the diagnostic work-up of juvenile Parkinsonism associated with epilepsy.
A second interesting finding in our patient is the alteration in ERG with nearly absent a and b responses,

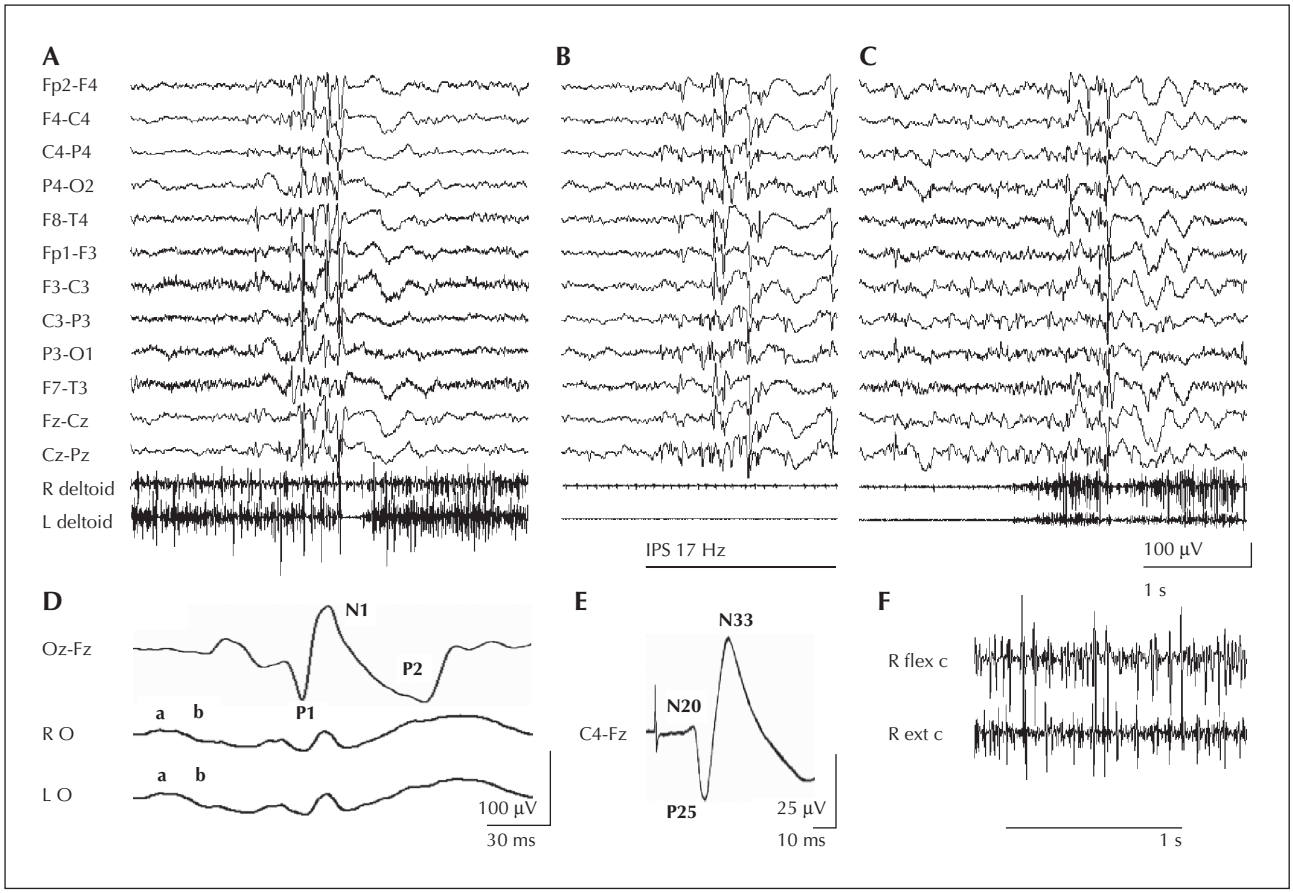

Figure 1. (A-C) EEG samples showing diffuse polyspike discharge followed by diffuse slow waves, associated with ictal myoclonia-atonia (A), photoparoxysmal response to intermittent photic stimulation (IPS, at 17 Hz) (B), and multifocal and diffuse spikes (C). (D) Flash-VEPs (top trace), and ERG responses (lower traces). Note increased amplitude of VEP responses and attenuated ERG a and b waves. (E) SEPs. Note giant P25-N33 response. (F) EMG sample from upper limb muscles showing low-amplitude and short myoclonic bursts.

consistent with the generalized dysfunction of both rod photoreceptors and rod bipolar cells. Attenuation of electroretinal response has been recently reported in LD patients with normal funduscopic and normal imaging retinal examination (Vincent *et al*., 2018). The presence of retinal dysfunction on ERG, especially when associated with giant VEP, may be a supportive feature in the diagnosis of LD. Moreover, as suggested by Vincent and co-workers, retinal impairment might serve as a non-invasive tool to monitor LD progression, and may potentially be a biomarker for therapeutic trials, at least in a subset of patients.

Finally, regarding the rare genetic variant, our patient from Senegal was shown to harbour a c.560A>C mutation in the *NHLRC1* gene, which has been previously reported only in two sibs from the bordering country, Mali (Traoré *et al*., 2009). Our report adds to the few cases of LD from African countries and may suggest a geographic-specific distribution of the different mutations associated with the disease. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

The present work was supported by the Italian Ministry of Health Ricerca Finalizzata Giovani Ricercatori 2010 (Project GR-2010-2304834 to JCD) and Ricerca Finalizzata Giovani Ricercatori 2016 (Project GR-2016-02363337 to JCD) and grants from the Pierfranco and Luisa Mariani Foundation (to TG).

None of the authors have any conflict of interest to declare.

References

Canafoglia L, Ciano C, Panzica F, *et al*. Sensorimotor cortex excitability in Unverricht-Lundborg disease and Lafora body disease. *Neurology* 2004; 63(12): 2309-15.

Franceschetti S, Michelucci R, Canafoglia L, *et al*. Progressive myoclonic epilepsies: definitive and still undetermined causes. *Neurology* 2014; 82(5): 405-11.

Gökdemir S, Cağlayan H, Kızıltan M, Karaağaç N, Leblebici C, Yeni SN. Presentation of an unusual patient with Lafora disease. *Epileptic Disord* 2012; 14(1): 94-8.

Hajnsek S, Petelin Gadze Z, Borovecki F, *et al*. Vagus nerve stimulation in Lafora body disease. *Epilepsy Behav Case Rep* 2013; 1: 150-2.

Lynch DS, Wood NW, Houlden H. Late-onset Lafora disease with prominent parkinsonism due to a rare mutation in EPM2A. *Neurol Genet* 2016; 2(5): e101.

Niemann N, Jankovic J. Juvenile parkinsonism: Differential diagnosis, genetics, and treatment. *Parkinsonism Relat Disord* 2019; 67: 74-89.

Traoré M, Landouré G, Motley W, *et al*. Novel mutation in the NHLRC1 gene in a Malian family with a severe phenotype of Lafora disease. *Neurogenetics* 2009; 10: 319-23.

Van Heycop Ten Ham MV. Lafora disease, a form of progressive myoclonus epilepsy. *Handb Clin Neurol* 1974; 15: 382-422.

Vincent A, Macrì A, Tumber A, *et al*. Ocular phenotype and electroretinogram abnormalities in Lafora disease: a "window to the brain". *Neurology* 2018; 91(3): 137-9.

Yildiz EP, Yesil G, Ozkan MU, Bektas G, Caliskan M, Ozmen M. A novel EPM2A mutation in a patient with Lafora disease presenting with early parkinsonism symptoms in childhood. *Seizure* 2017; 51: 77-9.

TEST YOURSELF

(1) In the complex presentation of Lafora disease, can Parkinsonism be counted among the most common symptoms?

(2) In Lafora disease, evoked potentials typically increase in amplitude. Describe the electroretinogram (ERG) response?

(3) In Lafora disease, what are the typical features based on EEG recordings?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".