

University of Groningen

Unusual course of Lafora disease

Zutt, Rodi; Drost, Gerrie; Vos, Yvonne; Elting, J.W.J.; Miedema, I.; de Koning-Tijssen, Marina. A. J.; Brouwer, Oebele; de Jong, Bauke M.

Published in:
epilepsia open

DOI:
[10.1002/epi4.12009](https://doi.org/10.1002/epi4.12009)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Zutt, R., Drost, G., Vos, Y., Elting, J. W. J., Miedema, I., tijssen, M., ... de Jong, B. M. (2016). Unusual course of Lafora disease. *epilepsia open*, 1(3-4), 136-139. DOI: 10.1002/epi4.12009

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Unusual Course of Lafora Disease

*Rodi Zutt, *Gea Drost, †Yvonne J. Vos, *Jan Willem Elting, *Irene Miedema,
*Marina A. J. Tijssen, *Oebele F. Brouwer, and *Bauke M. de Jong

Epilepsia Open, 1(3-4):136–139, 2016
doi: 10.1002/epi4.12009



Rodi Zutt is a Movement Disorders Fellow at the University Medical Centre Groningen in the Netherlands.

SUMMARY

A 42-year-old male was admitted for refractory status epilepticus. At the age of 25, he had been diagnosed with juvenile myoclonic epilepsy. He had a stable clinical course for over a decade until a recent deterioration of behavior and epilepsy. After exclusion of acquired disorders, diagnostic work-up included application of next-generation sequencing (NGS), with a gene panel targeting progressive myoclonic epilepsies. This resulted in the diagnosis Lafora disease resulting from compound heterozygous *NHLRC1* pathogenic variants. Although these pathogenic variants may be associated with a variable phenotype, including both severe and mild clinical course, the clinical presentation of our patient at this age is very unusual for Lafora disease. Our case expands the phenotype spectrum of Lafora disease resulting from pathogenic *NHLRC1* variants and illustrates the value of using NGS in clinical practice to lead to a rapid diagnosis and guide therapeutic options.

KEY WORDS: Myoclonus epilepsy, Refractory status epilepticus, Lafora disease, Next-generation sequencing.

Early-onset myoclonic epilepsy points toward a genetic disorder.¹ The most common epileptic myoclonus syndrome is juvenile myoclonic epilepsy (JME), which is occasionally associated with pathogenic variants in *GABRA1*, *CLCN2*, or *EFHC1*.^{2,3} It appears around puberty, remains stationary over time, and is characterized by bilateral irregular myoclonic jerks of predominantly the arms, particularly on awakening, while generalized tonic-clonic seizures (GTCS) or absences may occur.⁴ Other epilepsy syndromes with myoclonus with a progressive course include progressive myoclonic epilepsies (PMEs)¹ and inborn errors of

metabolism, including mitochondrial disorders. Lafora disease, a common form of PME, is characterized by adolescent onset (between 8 and 18 years) of progressive myoclonus combined with seizures, visual hallucinations, and cognitive decline. Lafora disease is inherited in an autosomal recessive fashion and is caused by pathogenic variants in the *EPM2A* or *NHLRC1* (also called *EPM2B*) genes, encoding the interacting proteins laforin and malin. Death occurs usually within 10 years after onset, although pathogenic *NHLRC1* variants are sometimes associated with a later age at onset and milder clinical course.^{5–7} Diagnosis of Lafora disease can be made by detection of polyglucosan aggregates in myoepithelial cells surrounding sweat glands, also called Lafora bodies.⁸ However, distinguishing Lafora bodies from normal apocrine cell granules may be difficult,⁹ making genetic testing the preferred diagnostic method. Genetic analysis with targeted next-generation sequencing (NGS) has changed diagnostic strategies for heterogeneous diseases associated with such a broad phenotype as epileptic myoclonus syndromes.¹⁰ It enables screening for pathogenic variants associated with PMEs, with results available in 4 weeks. Costs are comparable to those of sequencing three individual genes.^{11,12} Here, we describe a 42-year-old

Accepted July 6, 2016.

*Department of Neurology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands; and †Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands

Address correspondence to Bauke M. de Jong, Department of Neurology, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, the Netherlands. E-mail: b.m.de.jong@umcg.nl

© 2016 The Authors. *Epilepsia Open* published by Wiley Periodicals Inc. on behalf of International League Against Epilepsy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

male patient, initially diagnosed with JME, who appeared to have Lafora disease. Most remarkable was the unusual clinical course with very late adult onset and disease progression only after 17 years.

CASE REPORT

This 42-year-old male was admitted with a generalized convulsive status epilepticus. At age 25, he had had a single unprovoked GTCS, followed 2 years later by mild multifocal myoclonic jerks, mainly distally in his arms. Family history was negative for epilepsy. Electroencephalogram (EEG) at that time showed frequent generalized 2- to 3-Hz (poly)spike waves without photosensitivity, and a diagnosis of JME was made. With valproate treatment, myoclonic jerking persisted without seizures. Personal and social functioning appeared normal until a few weeks before admission, when friends noticed manic behavior.

Despite standard antiepileptic drug treatment, seizures persisted, requiring intubation and sedation with propofol and midazolam. After tapering sedation, tonic-clonic seizures and myoclonus of his feet reappeared. EEG showed continuous generalized spikes and high-voltage sharp waves with a bifrontocentral maximum. Sedation was restarted to induce electrographic burst suppression, and lacosamide was added. After 48 h of burst suppression, tapering of sedation again led to myoclonus of the feet and reappearance of epileptic paroxysms in the EEG. Subsequently, burst suppression with thiopental was maintained for another 48 h. After regaining consciousness 5 days later, the patient developed action-provoked and stimulus-sensitive multifocal myoclonus in his face (predominant left-sided) and distal limbs. Without an obvious EEG correlate, the cortical origin was substantiated with back averaging (Fig. 1A). Somatosensory evoked potentials (SEPs) showed no enlarged late potential complex (P27/N30), possibly owing to medication. The following days, still artificially ventilated, he responded adequately with normal facial and oculomotor functions while voluntary limb control was strongly impaired. This progressed into tetraparesis with continuously myoclonic limb jerking. A week later, convulsive status epilepticus reappeared with facial myoclonus and tonic-clonic seizures. EEG showed continuous generalized spikes and high-voltage sharp waves with a (right) frontocentral maximum. Under propofol, valproate was switched to gabapentin and phenytoin, clonazepam, levetiracetam, and lacosamide treatment was continued. His epilepsy finally became controlled and limb motor function gradually improved, with residual cognitive impairment, including mild expressive aphasia.

Initially, the status epilepticus was assumed to be related to JME. His long-lasting stable clinical course seemed a strong argument against PME. The differential diagnosis of refractory seizures preceded by behavioral changes included infectious or immune-mediated (paraneoplastic)

encephalopathy or an inborn metabolic error. Serum and cerebrospinal fluid analyses excluded infectious and immune-mediated etiologies. Brain MRI made 5 days after admission showed brain atrophy with T2 hyperintensity of midcingulate gray matter. Three weeks later, MRI abnormalities extended frontally (right) and occipitotemporally. This suggested a local consequence of epileptic activity, which was supported by T2 normalization on 3-month follow-up MRI (Fig. 1B). With a targeted NGS epilepsy panel, we screened for 19 monogenic PME-associated disorders, including Unverricht-Lundborg disease, Lafora disease, and neuronal ceroid lipofuscinoses. We identified two pathogenic variants in the *NHLRC1* gene (NM_198586.2) on chromosome 6p22, c.386C>A p.(Pro129His) and c.361G>A p.(Gly121Ser), pointing toward Lafora disease. The parents were not available to check their mutation status. Owing to the fact that the variants are close to each other, that the gene is analyzed by reads of about 150 bp long, and that both alleles are sequenced, we could assign the variants to different alleles. The diagnosis was confirmed by an axillary biopsy showing pathognomonic inclusion bodies in myoepithelial cells surrounding the sweat glands (Fig. 1C).

DISCUSSION

This case report describes a patient with Lafora disease following an atypical clinical course with late onset and long-lasting clinically stable course with sudden deterioration into refractory status epilepticus at the age of 42 years. The *NHLRC1* gene variants detected in our patient are considered pathogenic based on a number of arguments. Both variants are found only once in the publicly available control population database (Exome Aggregation Consortium; <http://exac.broadinstitute.org/>): p.Pro129His 1/116492 alleles and p.Gly121Ser 1/112232 alleles. The variants are part of one of the six NHL domains of the protein, a conserved domain probably involved in protein-protein interaction. Pro129 and Gly121 are both highly conserved amino acids. Alamut (version 2.6) from Interactive Biosoftware (<http://www.interactive-biosoftware.com>) was used to predict pathogenicity. It includes Align GVDG, SIFT, PolyPhen-2, and Mutation Taster. All four programs predicted the variants damaging the protein structure and function. Finally, both variants were published previously in patients with Lafora disease.^{5,6,13} Because segregation analysis in the family of our patient was not possible, the diagnosis of Lafora disease was confirmed by immune histochemical testing.

Later age at onset and milder clinical course are described in patients with pathogenic *NHLRC1* variants, resulting in lower neurologic disability scores and less severe seizure phenotype compared with patients with pathogenic *EPM2A* variants.^{5,14} However, to our knowledge, no patient with an initially mild disease presentation suddenly deteriorating toward refractory status epilepticus after more than 15 years has been described before.

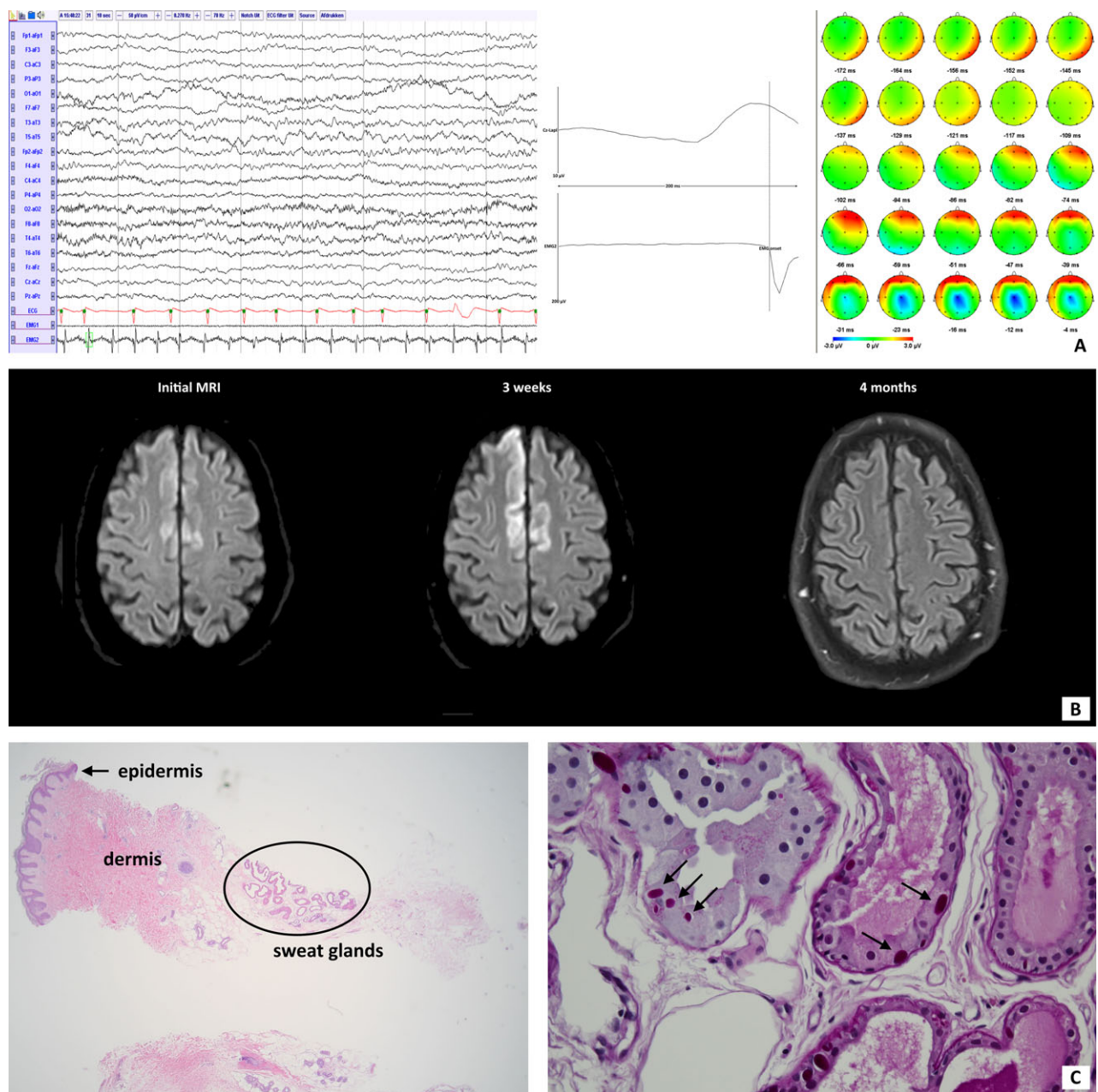


Figure 1.

Diagnostic investigations of patient with Lafora disease. **(A)** The left panel shows 8 s of raw EEG and electromyography (EMG) data of muscles of the right leg. Note the short duration of the EMG bursts. The EEG shows no epileptic abnormalities. The middle panel shows a clear positive-negative potential in the central electrode after back averaging, which starts approximately 40 ms before myoclonus onset. Right panel: Topographic mapping of the cortical potential. **(B)** Three consecutive brain MRIs (transversal sections). The left and middle slices show diffusion weighted images (DWIs); the right image is based on fluid attenuation inversion recovery (FLAIR) sequences. The first MRI shows hyperintensity of the gyrus cinguli corresponding to the maximum of seizure activity. The second MRI shows extension of the gray matter abnormalities likely associated with repeated periods of epileptic seizure activity. The third MRI shows complete disappearance of the abnormal T2 hyperintensity of the gray matter. **(C)** The left panel shows a hematoxylin and eosin (H&E) stain overview of the axillary biopsy. The right panel shows a detailed periodic acid Schiff staining with multiple Lafora bodies (arrows) in the myoepithelial cells surrounding the glands.

Epilepsia Open © ILAE

The characteristic visual hallucinations were not present in our case, which, on the other hand, is in accord with the study of Ferlazzo et al.⁵

Mild brain atrophy has been described in 35–40% of patients with typical and mild Lafora disease with normal MRI in the remaining patients.^{5,14} The transient MRI

abnormalities of our patient may well have been caused by the intensive seizure activity because they were localized in the area with the highest seizure activity registered on EEG and had normalized after 3-month follow-up. Transient MRI abnormalities with diffusion restriction have been described previously in patients with focal status epilepticus.¹⁵

Our case thus expands the phenotypic spectrum of Lafora disease due to pathogenic *NHLRC1* variants and highlights the importance of NGS in epileptic myoclonus syndromes.

DISCLOSURE OF CONFLICTS OF INTEREST

M.A.J. Tijssen has received educational grants from Actelion, Allergan, Ipsen, Medtronic, and Merz. O.F. Brouwer has received educational grants (UCB Pharma, Nutricia) and has presented lectures at sponsored meetings (UCB Pharma). The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

- Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. *Nat Rev Neurol* 2015;11:687–697.
- Duron RM, Medina MT, Martinez-Juarez IE, et al. Seizures of idiopathic generalized epilepsies. *Epilepsia* 2005;46(Suppl. 9):34–47.
- Delgado-Escueta AV. Advances in genetics of juvenile myoclonic epilepsies. *Epilepsy Curr* 2007;7:61–67.
- Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;30:389–399.
- Ferlazzo E, Canafoglia L, Michelucci R, et al. Mild Lafora disease: clinical, neurophysiologic, and genetic findings. *Epilepsia* 2014;55:e129–e133.
- Lohi H, Turnbull J, Zhao XC, et al. Genetic diagnosis in Lafora disease: genotype-phenotype correlations and diagnostic pitfalls. *Neurology* 2007;68:996–1001.
- Turnbull J, Girard JM, Lohi H, et al. Early-onset Lafora body disease. *Brain* 2012;135:2684–2698.
- Franceschetti S, Michelucci R, Canafoglia L, et al. Progressive myoclonic epilepsies: definitive and still undetermined causes. *Neurology* 2014;82:405–411.
- Andrade DM, Ackerley CA, Minett TS, et al. Skin biopsy in Lafora disease: genotype-phenotype correlations and diagnostic pitfalls. *Neurology* 2003;61:1611–1614.
- de Koning TJ, Jongbloed JD, Sikkema-Raddatz B, et al. Targeted next-generation sequencing panels for monogenetic disorders in clinical diagnostics: the opportunities and challenges. *Expert Rev Mol Diagn* 15:61–70.
- Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. *Epilepsia* 2012;53:1387–1398.
- Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. *Hum Mutat* 2013;34:1721–1726.
- Lesca G, Boutry-Kryza N, de Toffol B, et al. Novel mutations in EPM2A and NHLRC1 widen the spectrum of Lafora disease. *Epilepsia* 2010;51:1691–1698.
- Baykan B, Striano P, Gianotti S, et al. Late-onset and slow-progressing Lafora disease in four siblings with EPM2B mutation. *Epilepsia* 2005;46:1695–1697.
- Di Bonaventura C, Bonini F, Fattouch J, et al. Diffusion-weighted magnetic resonance imaging in patients with partial status epilepticus. *Epilepsia* 2009;50(Suppl. 1):45–52.