LATE DIAGNOSIS OF CEREBRAL FOLATE DEFICIENCY: FEWER SEIZURES WITH FOLINIC ACID IN ADULT SIBLINGS

Cerebral folate deficiency is a genetically heterogeneous condition. Mutations in FOLRI are responsible for a rare but treatable form of cerebral folate deficiency (OMIM #613068). The gene codes for folate receptor alpha (FRα), a specific CNS folate transporter. Individuals with FOLRI-related folate deficiency present with ataxia, dyskinesia, spasticity, seizures, and regression in cognitive abilities and motor skills during early childhood. Seizures commonly observed include generalized tonic-clonic, atonic, and myoclonic. To date, there have been 18 individuals with FOLRI-related cerebral folate deficiency diagnosed in childhood and reported in the literature. Early diagnosis is crucial, as high-dose folinic acid (2–5 mg/kg/day) has been reported to be an effective treatment that can ameliorate or even prevent further neurodegeneration, although no long-term treatment studies have been performed. We present the late diagnosis of adult siblings with cerebral folate deficiency due to FOLRI mutations and their subsequent treatment.

The eldest sibling (sibling 1), aged 33 years, met her early developmental milestones until 22 months of age, when she developed myoclonic seizures, ataxia, and developmental regression. At 15 years of age, she had learned 75–100 words, but this decreased to only 12 words by age 30 years. By 7 years of age, she was wheelchair-dependent. There was a period of remission of her seizures from 11 to 18 years of age, but the generalized tonic-clonic seizures recurred in her 20s, particularly during sleep. As an adult, she had an average of 1 seizure per day and was treated with gabapentin.

Her younger sister (sibling 2), aged 28 years, is more severely affected. She also had a period of normal development until 18 months of age, when she developed progressive ataxia and developmental regression. This was followed by myoclonic seizures that evolved to generalized tonic-clonic seizures. She had feeding difficulties and required gastrostomy tube placement. She was also wheelchair-dependent by 5 years of age. She developed only a few words of speech, although she has some receptive language. Her condition stabilized in her teens, but she made no developmental progress. During her 20s, her motor function gradually declined and she had an average of 1 seizure daily, particularly during sleep, and she is treated with carbamazepine and levetiracetam. An MRI of sibling 2 (at age 25 years) showed extensive periventricular and deep cerebral white matter changes with frontal lobe and cerebellar atrophy (figure).

There was no family history of intellectual disability or epilepsy. There are 3 unaffected sisters, and the parents are first cousins of Italian ethnic origin.

The siblings were recruited into the national Care4Rare research project to identify the genetic etiology of their disease using whole-exome sequencing, and informed consent was obtained from the family. A novel homozygous mutation in FOLRI, NM_016724, c.128A>G, p.H43R was identified in both siblings. The parents were confirmed to be heterozygous carriers, and neither of the unaffected sisters was homozygous for the variant. The variant was not present in control databases, and in silico prediction programs (SIFT, PolyPhen-2) predicted it to be pathogenic. CSF studies in sibling 2 demonstrated diminished 5-methyltetrahydrofolate at <10 nmol/L (reference: 40–120 nmol/L) and reduced homovanillic acid at 26 nmol/L (reference: 145–324 nmol/L), consistent with cerebral folate deficiency. Oral folinic acid replacement was promptly initiated at 2 mg/kg/day. This resulted in a reduction in seizure frequency by approximately half. In sibling 2, seizures reduced from an average of 42 (range: 18–73) per month to 20 (range: 12–26) per month (t-test, one-sided, p = 0.000006), and in sibling 1 seizures reduced from 20 (range: 7–37) per month to 13 (range: 2–36) per month (t-test, one-sided, p = 0.012). Sibling 1 showed an increase in her vocalizations and use of words and improved fine motor skills, and sibling 2 appeared more alert. The dose of antiepileptic medication has been reduced for both sisters. The late molecular diagnosis of a treatable cause of seizures and intellectual disability in these adult siblings demonstrates the potential impact of next-generation sequencing for early diagnosis to inform disease-altering therapy. Although initiated later in life than has previously been reported, treatment with folinic acid showed a marked reduction in the frequency of seizures for both siblings, improving...
their quality of life and permitting a reduction in doses of antiepileptic medication. The molecular diagnosis also enabled accurate recurrence risk counseling for family members seeking information for family planning. This case highlights the value of a molecular diagnosis for adults with epilepsy and the finding that even late initiation of treatment for FOLR1 deficiency provides important benefits.7

From the Division of Medical Genetics (P.F.), Alberta Children’s Hospital, Calgary, Alberta, Canada; Department of Genetics (S.M.L., S.L.S., K.M.B., D.A.D.) and Department of Radiology (J.D., D.A.D.) Children’s Hospital of Eastern Ontario, Ottawa, Canada; and Children’s Hospital of Eastern Ontario Research Institute (K.M.B.), University of Ottawa, Canada.

Coinvestigators are listed on the Neurology® Genetics Web site at Neurology.org/ng.

Author contributions: Dr. Patrick Ferreira contributed to drafting/revising the manuscript for content, study design, and interpretation of data as well as acquisition of data. Stephanie M. Luco was involved in drafting/revising the manuscript for content, study design, and interpretation as well as statistical analysis. Dr. Sarah L. Sawyer contributed drafting/revising the manuscript for content as well as acquisition of data. Dr. Jorge Davila contributed to analysis of data and drafting/revising the manuscript for content. Dr. Kym M. Boycott contributed to drafting/revising the manuscript for content, study design, and analysis of data. Dr. David A. Dyment contributed to drafting/revising the manuscript for content, study design, and analysis of data.

Acknowledgment: The authors thank the family for their generosity in participating in this work.

Study funding: This study was performed as part of the Care4Rare Canada Consortium funded by Genome Canada, the Canadian Institutes of Health Research, the Ontario Genomics Institute, Ontario Research Fund, Genome Quebec, and Children’s Hospital of Eastern Ontario Foundation. D.A.D. is the recipient of a CIHR clinical investigators award.

Disclosure: Dr. Patrick Ferreira, Stephanie M. Luco, Dr. Sarah L. Sawyer, Dr. Jorge Davila, Dr. Kym M. Boycott, and Dr. David A. Dyment report no disclosures relevant to the manuscript. Go to Neurology.org/ng 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 October 12, 2015. Accepted in final form October 23, 2015.

Correspondence to Dr. Dyment: ddyment@cheo.on.ca


(A) Axial fluid-attenuated inversion recovery image showing extensive white matter disease and sparing of U-fibers. (B) Atrophy of frontal hemispheres and cerebellum with sparing of temporal lobes.
Late diagnosis of cerebral folate deficiency: Fewer seizures with folinic acid in adult siblings
Patrick Ferreira, Stephanie M. Luco, Sarah L. Sawyer, et al.
Neurol Genet 2016;2:
DOI 10.1212/NXG.0000000000000038

This information is current as of December 23, 2015
| Updated Information & Services | including high resolution figures, can be found at:  
http://ng.neurology.org/content/2/1/e38.full.html |
| Supplementary Material | Supplementary material can be found at:  
http://ng.neurology.org/content/suppl/2015/12/23/2.1.e38.DC1  
http://ng.neurology.org/content/suppl/2016/02/22/2.1.e38.DC2 |
| References | This article cites 7 articles, 0 of which you can access for free at:  
http://ng.neurology.org/content/2/1/e38.full.html##ref-list-1 |
| Subspecialty Collections | This article, along with others on similar topics, appears in the following collection(s):  
**All Epilepsy/Seizures**  
http://ng.neurology.org/cgi/collection/all_epilepsy_seizures  
**All Genetics**  
http://ng.neurology.org/cgi/collection/all_genetics  
**All Pediatric**  
http://ng.neurology.org/cgi/collection/all_pediatric  
**Metabolic disease (inherited)**  
http://ng.neurology.org/cgi/collection/metabolic_disease_inherited |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
http://ng.neurology.org/misc/about.xhtml#permissions |
| Reprints | Information about ordering reprints can be found online:  
http://ng.neurology.org/misc/addir.xhtml#reprintsus |