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Letter

Hot water epilepsy and *SYN1* variants

To the Editors:

We read with great interest the article "X-Linked Focal Epilepsy With Reflex Bathing Seizures: Characterization of a Distinct Epileptic Syndrome" by Nguyen et al.[1] The authors described several males from a large family with focal reflex seizures triggered by contact with water, learning disabilities and/or autism, and a nonsense pathogenic variant in *SYN1* (Xp11.3-p11.2).

We had previously characterized the electroclinical manifestations of a family affected by childhood onset hot water epilepsy (HWE), subsequently followed by nonreflex seizures.[2] The proband presented with focal seizures during contact with water at age 8 years. The episodes—occurring especially after hot water had been poured on his body—were characterized by a sensation of rising heat, dystonic posture of unilateral limbs, and cyanosis of the lips, followed by oral automatisms and inability to speak. Ictal electroencephalography (EEG) was characterized by bilateral rhythmic theta activity over the frontocentral and vertex regions. Three years after seizure onset, he exhibited nonreflex seizures consisting of a tingling ascending sensation starting from the lower limbs. His maternal uncle showed the same epileptic phenotype. Despite normal but below average intelligence quotient (80), the proband showed learning disability involving reading, writing, and calculation, and his maternal uncle exhibited mild intellectual disability (ID).

We recently performed whole exome sequencing (WES) in this family and identified a splice-site pathogenic variant in *SYN1* (NM_133499.2: c.527+1G>T). This variant segregates with the disease (present in proband, mother, and maternal uncle, absent in father; Figure 1) and is absent from the ExAc browser, ClinVar, and 1000 Genomes. Analysis of the splice donor mutation (GCGgtgagt to GCGttgagt) using the Human Splice Finder tool (http://www.umd.be/HSF3/, PMID 1933 9519) revealed a significant decrease in donor site score from 92% to 66% (position weight matrix algorithm) and the potential preference of a cryptic donor site five nucleotides upstream (GTCgtgcgt), thus leading to a shift in the reading frame. Prior testing of *SCN1A* produced normal results,[2] and WES did not identify other pathogenic or likely pathogenic variants affecting genes that have been previously associated with epilepsy/seizures in humans or mice.

The pathogenesis of reflex seizures caused by contact with water is largely unknown, with proposed loci on chromosomes 4 and 10[1] and a family with a variant in *SLC1A1*[3] that was, however, present at a low frequency in the general population.

The male:female ratio of 2.5:1 supports the findings by Nguyen et al[1] and ours in favor of the hypothesis that HWE is caused by an X-linked gene—such as *SYN1*—in a significant proportion of individuals. Although bathing seizures and HWE have been considered different entities by some authors in the past, the similar ictal semiology and EEG in individuals with the same genetic cause, despite the slight difference in the trigger (hot vs cold water), suggest that these conditions are part of the same spectrum.

Clonic or generalized seizures may occur after a bath also in patients with Dravet syndrome at epilepsy onset, and one may think of *SCN1A* as a possible candidate gene, as we did when testing this gene first. However, the epileptic phenotype of patients with Dravet syndrome is usually characterized by more complex features such as prolonged uni- or bilateral convulsive febrile seizures, followed by afebrile seizures and slowing of psychomotor development.[4]

The update on our family demonstrates that additional pathogenic variants in *SYN1* cause seizures triggered by contact with water, and we strongly agree with Nguyen et al[1] that this is a distinctive epileptic syndrome. Based on the nine patients with extensive and reliable evaluation described thus far,[1,5] the phenotype can thus be described as follows:

1. Focal onset reflex seizures triggered by contact with water with onset in the first 2 decades of life represent the core phenotype, with or without ID/learning disability and intrafamilial variability;
2. Nonreflex seizures follow the initial presentation in 16%-38% of individuals,[1] with good response to antiepileptic treatment, and self-induced seizures are not uncommon; and
3. Ictal EEG is characterized by rhythmic theta activity over the frontocentral/temporal regions.

By review of the literature, we also noticed that truncating mutations are associated with reflex seizures triggered by contact with water,[1,5] whereas the majority of patients affected by only neurodevelopmental diseases (autism/behavioral problems/ID) have missense variants. Therefore, we infer that different types of mutations cause different phenotypes, with truncating variants having an effect on firing/bursting activity, as suggested by functional studies.[6,7]

In conclusion, our update expands the phenotype of *SYN1*-related disorders, which represent a unique and recognizable condition. Epilepsy triggered by contact with

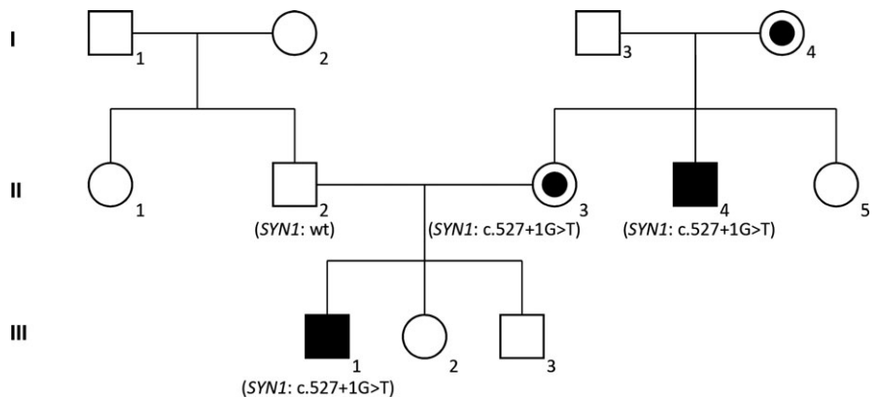

FIGURE 1 Pedigree of the family showing an X-linked inheritance pattern. Black squares denote affected males; dotted circles indicate unaffected female carriers. wt, wild type. The pathogenic variant is reported in parentheses below the family members who were tested; males are hemizygous, and females are heterozygous for the variant. Individual I-4 is an obligate carrier and presumed to harbor the heterozygous variant, although she was not directly tested (modified from Vignoli et al[2])

water is a new and exciting area of research, and we encourage colleagues to test patients with this distinctive phenotype for *SYN1* mutations, to clarify the hypotheses raised by our commentary.

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DISCLOSURE

The authors have no conflicts of interest to report. 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.

Keywords

bathing seizures, hot water epilepsy, reflex seizures, *SYN1*, synapsins

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Announcements

Epilepsia – November 2018 – Announcements

1st Qatar International Epilepsy Course

7–12 November 2018
Doha, Qatar
Website: http://phunar.com/hamad/

KCL International Neurosurgical Conference 2018

10–11 November 2018
London, UK
Conference website: http://www.kclneurosurgery.co.uk/

Epilepsy, critical care & anaesthesia: the interface. A joint 1-day symposium

15 November 2018
ILAE British Chapter & The Neuroanaesthesia and Critical Care Society of Great Britain and Ireland
Website: https://ilaebritish.org.uk/events/epilepsy-critical-care-anaesthesia-the-interface-a-joint-1-day-symposium/

Swedish Chapter National Meeting

15 November 2018
Lund, Sweden

Nationaal Epilepsie Symposium

16 November 2018
Jaarbeurs, Utrecht, Netherlands
http://www.epilepsieliga.nl/Congressen-en-Symposia/6/32/0/363/Nationaal-Epilepsie-Congres-/

3ème Session des Ecoles EEG & EMG (SMNPH 2018)

16–18 November 2018
Fès, Morocco
http://www.apnec.ma/smnph2018/

2018 AES Annual Meeting

30 November–4 December 2018
New Orleans, Louisiana, USA
American Epilepsy Society website: https://www.aesnet.org/

9th EPODES Advanced I

21–25 January 2018
Brno, Czech Republic
Congress website: http://www.ta-service.cz/epodes2019/

Seizures and Stroke 2019

20–22 February 2019
Gothenburg, Sweden
Website: https://seizuresandstroke.com/

5th East Mediterranean Epilepsy Congress

7–9 March 2019
Marrakech, Morocco

20th Joint Annual Conference of the Indian Epilepsy Society and Indian Epilepsy Association (ECON 2019)

8–10 March 2019
New Delhi, India
http://www.econ2019.org/

EEG in the First Year of Life – From newborn to toddler

25–28 March 2019
Cambridge, UK
Information: https://www.ilae.org/congresses/eeg-in-the-first-year-of-life

13th World Congress on Controversies in Neurology (CONy)

4–7 April 2019
Madrid, Spain
Congress website: http://comtecmed.inwise.net/CONyCongress2019

7th London-Innsbruck Colloquium on Status Epilepticus & Acute Seizures

7–9 April 2019
London, UK
Congress website: https://statusepilepticus.eu/index.php

6th Residential International Course on Drug Resistant Epilepsies

5–11 May 2019
Rome, Italy
More information: https://www.ilae.org/congresses/6th-residential-international-course-on-drug-resistant-epilepsies

Annual Meeting of the Austrian and German Societies for Epileptology and the Swiss Epilepsy League ("Dreilaendertagung")

8–11 May 2019
Basel, Switzerland
www.epi.ch/fach

XV | Workshop on Neurobiology of Epilepsy (WONOEP 2019)

16–20 June 2019
Ayutthaya, Thailand
Satellite session of the 33rd IEC: http://internationalepilepsycongress.org/wonoep

33rd International Epilepsy Congress

22–26 June 2019
Bangkok, Thailand
Website: http://internationalepilepsycongress.org/

2019 Advanced San Servolo Epilepsy Course

7–18 July 2019
San Servolo, Venice, Italy
Information and application: https://www.ilae.org/congresses/2019-advanced-san-servolo-epilepsy-course

4th African Epilepsy Congress

22–24 August 2019
Kampala, Uganda

5th Summer School on Imaging in Epilepsy (SuSIE)

25–28 August 2019
Bochum, Germany
Website: http://www.imaging-in-epilepsy.org/

2nd International Congress on Mobile Devices and Seizure Detection in Epilepsy

6–7 September 2019
Lausanne, Switzerland
http://www.mhsdepilepsy2019.com/