LETTER TO THE EDITOR

To The Editor

Acquired Microcephaly in a Patient with *HECW2* Mutation

Keywords: Epileptic encephalopathy, Microcephaly, Neurodevelopmental disorders

HECW2 mutations have been recently recognized as a cause of a neurodevelopmental disorder associated with early infantile seizures, severe global developmental delay, hypotonia, and cortical visual impairment (OMIM #617268). The disorder was originally described in 2016 after *HECW2* was identified as a candidate gene during exome sequencing in a patient with intellectual disability and epilepsy.[1] To date, 14 additional patients have been reported in the literature with severe phenotypes and similar features.[2–4]

Acquired microcephaly is a characteristic feature in a few well-described disorders, for example Rett syndrome and other neurodevelopmental syndromes caused by mutations in *MECP2*, *CDKL5*, *FOXG1, SLC9A6,* and *TCF4*.[5] Acquired microcephaly has not been documented in association with *HECW2* mutation. We describe a patient with *HECW2* mutation and acquired microcephaly accompanying a severe epileptic encephalopathy phenotype.

The patient, currently 3.5 years old, was born at 41 weeks following a spontaneous vaginal delivery after an uncomplicated pregnancy, labor, and delivery. Birthweight was 3.26 kg (~25th percentile), length 51cm (~50th percentile), and head circumference 34 cm (~25–50th percentile). She was discharged home after 2 days with no complications. There was no history of trauma or significant illness. There was no consanguinity. Family history was remarkable for Fragile X syndrome with the maternal grandmother being a known premutation carrier.

The patient presented at 3.5 months of age with developmental delay and a 1-week history of paroxysmal movements. On examination, there were no dysmorphic features or neurocutaneous stigmata. Cardiac, respiratory, and abdominal exam were normal. She did not fix or follow. Pupils were equal and reactive to light. Her extraocular, facial, and tongue movements were normal. She had central and peripheral hypotonia, displayed some spontaneous movements, and had normal reflexes. No tremor was noted.

Her paroxysmal movements had two distinct semiologies: First, episodes of body stiffening with extension of the legs and flexion of the elbows associated with decreased level of consciousness, lasting 15–25 seconds and occurring about 5–10 times/day. She also had shorter episodes in clusters, involving tonic eyelids closure and body stiffening lasting less than 1 second. The first was thought to be tonic seizures and the second infantile spasms. Electroencephalogram (EEG) showed hypsarhythmia with chaotic, large-amplitude slow background activity with frequent multifocal epileptiform activity, especially posteriorly (Figure 1A). She was started on vigabatrin, titrated up to 150 mg/kg/day, as well as Vitamin B6 250 mg daily.

There was a transient decrease in spasm frequency, but soon returned to the same seizure frequency and repeat EEG was unchanged. She subsequently underwent treatment trials with high-dose prednisolone (20 mg tid), topiramate (10 mg/kg/day), and ketogenic diet for the infantile spasms and then phenobarbital (5 mg/kg/day), CBD oil (artisanal, obtained by parents), levetiracetam (79 mg/kg/day), clonazepam (0.16 mg/kg/day), and divalproex sodium (40 mg/kg/day) for ongoing seizures. Her seizures remained intractable and frequent, ~10–20 seizures/day. Other clinical features included cortical visual impairment, hypotonia, severe developmental delay, and acquired microcephaly: Head circumference was 40.5, 43, and 44.3 cm at 3.5, 6.5, and 8.5 months of age, respectively (all ~50th percentile), 45.5 cm at age 15 months (~25–50th percentile), and 47 cm at age 35 months (just above 3rd percentile). Limbs' exam findings evolved over time to peripheral hypertonia, minimal spontaneous limb movements, brisk reflexes, and limbs clonus at last clinic follow-up at 35 months of age. Coordination could not be assessed due to her severe developmental delay. She is fed through a G-tube.

Repeat EEGs showed persistent hypsarhythmia, subsequently evolving to a pattern of multiple independent spike foci with slow spike-wave and sharp-and-wave (Figure 1B). Routine EEGs captured several brief tonic seizures and epileptic spasms. Brain magnetic resonance imaging (MRI) at 4 months of age was normal. Magnetic resonance spectroscopy showed small lactate peak over the left basal ganglia. Biochemical investigations were unrevealing, including electrolytes, lactate, ammonia, total and free carnitine, acylcarnitines, transferrin isoelectric focusing, very long chain fatty acids, plasma and urine amino acids, urine organic acids, serum total homocysteine, creatine kinase, biotinidase, urine α-Amino adipic semialdehyde, Batten screen (PPT1 and TPP1 enzyme activities), and CSF studies (glucose, lactate, amino acids, and neurotransmitters). A SNP-based chromosomal microarray (Combimatrix; Irvine, CA) was normal with no diagnostic copy number variants or regions of homozygosity. FMR1 repeat analysis was normal. Whole exome study (trio) was done given the high suspicion of an underlying genetic cause of her intractable epilepsy and developmental delay. A missense variant in *HECW2* was found, c.4485G>T (p. Arg1495Ser). This variant was *de novo* with maternity and paternity confirmed and has not been reported before in public databases. It was therefore classified as *likely pathogenic*.

The *HECW2* gene is located at 2q32.3. It codes for a HECT-type E3 ubiquitin-protein ligase. It is implicated in the regulation of several important pathways by inducing ubiquitination and alternatively stabilizing or tagging for degradation, p73 (cell cycle arrest and apoptosis), *AMOTL-1* (endothelial cell junctions), and PNCA/lamin B1 (nuclear organization).[6-8] There are no published data on animal models with mutations in *HECW2*.

Although the exact pathogenesis of *HECW2* dysfunction is still unknown, its effect on prenatal and postnatal neurodevelopment appears to be severe. All patients reported so far have severe-to-profound global developmental delay and 14/15 patients have epilepsy with a spectrum of controlled to

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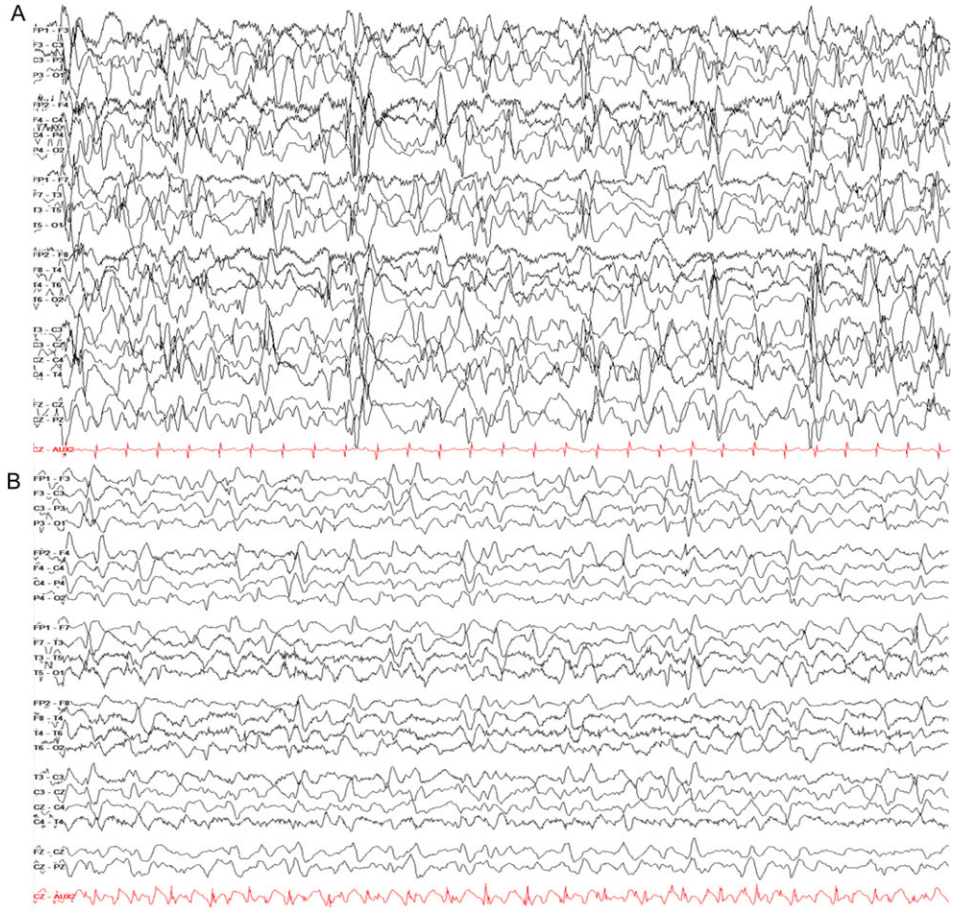

Figure 1: *EEG findings are shown in anterior–posterior bipolar montage; sensitivity 15 μV/mm, time base 30 mm/sec, LFF 1 Hz, HFF 70 Hz. (**A**) At 4 months of age showing hypsarhythmia with chaotic, very high amplitude slow waves and spike/sharp waves involving all cortical regions. (**B**) At 34 months of age showing high amplitude background activity with abundant multifocal independent spike-wave and slow spike-wave/sharp wave.*

intractable seizures.[4] Our patient has a severe seizure phenotype with frequent daily seizures.

Many genes have established roles in postnatal neurodevelopment through multiple molecular signaling pathways and neuronal receptors.[5] Diseases caused by mutations in these genes may explain the acquired microcephaly that is commonly seen, in addition to other features. Nakamura et al. previously reported a patient with *HECW2* mutation and a diagnosis of atypical Rett syndrome but without microcephaly.[3] Berko et al. included a female patient with *HECW2* mutation (#7),[2] who had a head circumference of 49.5 cm at age 6 years, documented as <3rd percentile; however, this value is ~10–25th percentile for age.[9] There is no evidence of acquired microcephaly in the reported cases and that is why Nakamura et al. concluded that absence of microcephaly in *HECW2* is an important differentiator from other known "Rett-like genes." Cortical atrophy has been demonstrated in other patients with *HECW2* mutations and serial MRI follow-up. Our patient had one MRI and no follow-up imaging to confirm atrophy.

Our patient presented with a severe neurodevelopmental phenotype including acquired microcephaly. Therefore, *HECW2* should be considered in the same category of genes with prominent postnatal neurodevelopmental effects and in the clinical context of severe developmental delay and epilepsy, with or without acquired microcephaly.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Consent

Verbal and written consent was obtained from the parents.

Ethics Approval

Ethics approval was obtained from the local Research Ethics Board of the University of Manitoba.

Statement of Authorship

TP did part of the literature search, wrote the first draft of the manuscript and was involved in revision of subsequent drafts

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AO selected and provided interpretation of samples of the patient's EEGs, wrote part of the case description, reviewed and critiqued the manuscript

PF was involved in provision of clinical care, reviewed and critiqued the manuscript

MSS was involved in the organization and execution of the project. He obtained written consent from the parents and obtained Ethics approval. He did part of the literature search, wrote part of the case description and discussion, revised the first draft, and edited the manuscript several times.

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