



University of Nebraska
Medical Center
Nebraska Medicine

Graduate Medical Education
Research Journal

Volume 4 | Issue 1

Article 31

July 2022

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Recommended Citation

Scheffler et al, J. L. Expanding the Phenotype of HNRNPU-related Disorders to Include Brief, Resolved, Unexplained Events (BRUE). Graduate Medical Education Research Journal. 2022 Jul 14; 4(1). <https://digitalcommons.unmc.edu/gmerj/vol4/iss1/31>

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Expanding the Phenotype of HNRNPU-related Disorders to Include Brief, Resolved, Unexplained Events (BRUE)

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Program: Genetics

Type: Case Report

Background: hnRNP-U deficiency is caused by pathogenic variants in HNRNPU, which encodes the heterogeneous nuclear ribonucleoprotein U (HNRNPU), a highly conserved protein responsible for assisting spliceosomes in mediating transcription and alternative splicing activity. HnRNPs are responsible for the regulation of translation at the presynaptic sites as well as the transportation of stabilized mRNAs along the axonal cytoskeleton.

Case: Here, we report a 2-year-old-male with a HNRNPU variant with a new presentation of apparent recurrent apneic spells with an underlying epileptic origin. These were described as apnea followed by desaturation and tachycardia in the 180's-200 range prior to resolution of symptoms. He also had autistic behaviors, hypotonia, global developmental delay, heart defects, and unique facial features. The anesthetist professional parents describe multiple BRUE.

At 26 months, he presented to the hospital with hypotonia and unique facial features, global developmental delay, autistic behaviors, dyspraxia with cognitive disability and a change in mental status. On physical exam, the proband had telecanthus, a broad nasal bridge, short palpebral fissures, mild nevus flammeus changes on his face, a single right palmar crease, and a modified single crease on the left. EKG showed a sinus rhythm with intermittent 1st degree AV block, blocked premature atrial contractions, left axis deviation, right bundle branch block, and an ejection fraction of 67%. Echocardiography re-identified an atrial septal defect. Brain MRI showed a T2/FLAIR hyperintense signal in the white matter of the parietal lobes, left greater than right. EEG identified generalized slowing indicative of mild nonspecific encephalopathy. The history of episodes was determined to be consistent with partial onset seizures with eye opening, deviation, and tachycardia with apnea and medical treatment ensued.

Genetic testing including microarray and an epilepsy panel identified no genomic dosage anomalies and a de novo nonsense mutation

(c.803+2T>C; p. unknown in HNRNPU), classified as pathogenic. Patient consent was obtained to use this case for educational purposes.

Conclusion: The study of hnRNP complexes has gained momentum in neurodegenerative and tumorigenesis disease research. hnRNPs have a key role in mediating transcription, alternative splicing, and translation activity. Recent research suggests 21 previously unreported probands; nearly doubling the recorded patient population. Probands in the literature to date have had variable presentation, but usually with hypotonia, global developmental delays, and seizures. This suggests the addition of HNRNPU to all seizure-related diagnostic panels. We would also recommend including the HNRNPU-related disorders in a differential diagnosis of BRUE and recurrent apneic episodes as any underlying clonic activity may be profoundly subtle. ■

<https://doi.org/10.32873/unmc.dc.gmerj.4.1.023>

Presurgical Evaluation of the Dominant Hemisphere Function in an Adolescent Patient with Rasmussen's Encephalitis using Magnetoencephalography

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Type: Case Report

Background: Rasmussen's encephalitis (RE) is a devastating progressive inflammatory disease causing debilitating neurological deficits and intractable focal epilepsy. The therapeutic benefits of hemispherectomy in RE have been well established at this time; however, some patients do not achieve optimal seizure control following the surgery. The reasons for such suboptimal outcomes have included the presence of bilateral epileptogenic foci and involvement of the

dominant language hemisphere leading to concerns regarding surgical implications on preserved cognition, motor functions and language. There are currently no effective diagnostic tools to provide quantitative data regarding the potential deficits from the disconnection procedures in patients with RE.

Case: We present a case of a 15-year-old male with RE, right hemiparesis, recurrent status epilepticus and Epilepsia Partialis Continua who was considered for functional hemispherectomy of the dominant hemisphere. Due to his low baseline ambulatory function, and inability to cooperate with WADA test requirements, the non-invasive magnetoencephalography

(MEG) functional study was performed. This provided quantitative assessment of the lateralization of his language function and of his motor cortical organization to derive predictions for post-operative deficits. Using a passive listening auditory language paradigm, developed at our institution, the cortical responses to verbal stimuli were recorded within 350-450 ms in the right hemisphere and 600 ms in the left hemisphere, suggesting that language function was represented bilaterally. The source localization analysis confirmed that response in the right hemisphere was localized to the temporal-parietal area (angular gyrus), while response in the left hemisphere was localized to the posterior middle temporal gyrus.