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Leigh Syndrome as a Phenotype of Near-Homoplasmic m.8344 A>G Variant in Children

Sam Nicholas Russo, MD[1], Amy Goldstein, MD[2,3], Amel Karaa, MD[4], Mary Kay Koenig, MD[1,5], and Melissa Walker, MD, PhD[6]

Abstract

In the field of mitochondrial medicine, correlation of clinical phenotype with mutation heteroplasmy remains an outstanding question with few, if any, clear thresholds corresponding to a given phenotype. The m.8344A>G mutation is most commonly associated with myoclonus epilepsy and ragged red fiber syndrome (MERRF) at varying levels of heteroplasmy. However, a handful of cases been previously reported in which individuals homoplasmic or nearly homoplasmic for this mutation in the blood have presented with multiple bulbar palsies, respiratory failure, and progressive neurologic decline almost uniformly following a respiratory illness. MRI brain in all affected individuals revealed symmetric T2 hyperintense lesions of subcortical gray matter structures, consistent with Leigh syndrome. Here, we present 3 cases with clinical, biochemical, and neuro-imaging findings with the additional reporting of spinal lesions. This new phenotype supports a heteroplasmy-dependent phenotype model for this mutation and recognition of this can help clinicians with diagnosis and anticipatory clinical guidance.

Keywords

mitochondria, MERRF, Leigh syndrome, heteroplasmy, homoplasmy, phenotype

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Introduction

Mitochondria are membrane-bound organelles present in all nucleated eukaryotic cells. Mitochondria create ATP for cellular energy via oxidative phosphorylation. The biology and genetics of mitochondrial oxidative phosphorylation are complex because the components that make up the structure and control the function of the mitochondria are encoded for by both mitochondrial and nuclear genomes. Any abnormality in these components can reduce the functional output of the oxidative phosphorylation system producing a wide range of diseases with characteristic, marked genetic and phenotypic heterogeneity, as well as significant pleiotropy. Pathogenic derangements have been described in either the mitochondrial or nuclear genomes. Recent literature details at least 300 disease-causing genes linked to mitochondrial dysfunction and this number continues to rise.[1] In cases of mitochondrial DNA inheritance there is added complexity due to heteroplasmy, i.e. the combination of mutated and wild-type mitochondrial DNA—which exists as a high copy number genome—within a single cell. The relationship between heteroplasmy in blood and other tissues is not clearly univariate and remains poorly understood.[2,3]

[1] Division of Child and Adolescent Neurology, Department of Pediatrics, The University of Texas McGovern Medical School, Houston, TX, USA
[2] Mitochondrial Medicine Frontier Program, Division of Human Genetics, Children's Hospital of Philadelphia, PA, USA
[3] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[4] Mitochondrial Disease Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[5] The University of Texas Mitochondrial Center of Excellence, Houston, TX, USA
[6] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Corresponding Author:
Sam Nicholas Russo, MD, The University of Texas McGovern Medical School, 6410 Fannin Street, Suite 732, Houston, TX 77030, USA.
Email: sam.n.russo@uth.tmc.edu

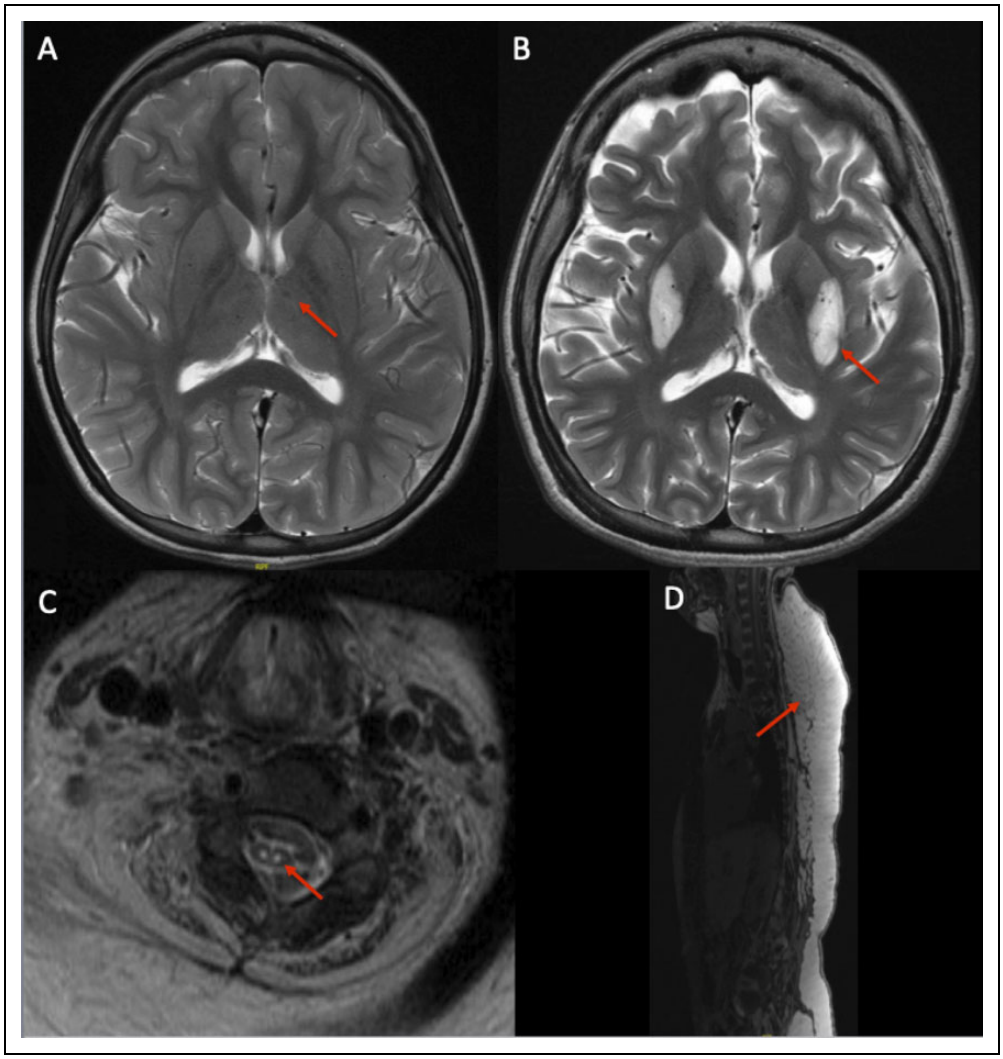

Figure 1. Case 1. A, T2 hyperintense thalamic lesion at age 7 years. B, Putaminal lesions at age 8 years. C, T2 hyperintense lesions of the cervical spine. D, Sagittal T1 image reveals marked posterior subcutaneous fat.

The m.8344A>G mutation is typically associated with myoclonus epilepsy with ragged red fibers (MERRF). MERRF, as the name suggests, is defined by the presence of myoclonus, generalized epilepsy, ataxia, and ragged red fibers on muscle biopsy. Development in early childhood is typically normal; only 15-25% have cognitive impairment at diagnosis. Importantly, neuro-anatomic abnormalities are not a diagnostic or common finding in MERRF.[4]

By contrast, Leigh syndrome is a progressive neurodegenerative mitochondrial disorder and the most common pediatric mitochondrial disease phenotype. It is clinically defined by bilateral, symmetric T2-hyperintense lesions of the brainstem and basal ganglia, associated, appropriately localizing neurologic symptoms, developmental delay, and elevated serum or cerebral spinal fluid (CSF) lactate.[5] Classically, symptoms first appear within the first 12 months of life and patients succumb to respiratory failure on average by age two.[6,7] To date, over 75 genes, located both in the nuclear and mitochondrial genomes, have been linked to Leigh syndrome.[5] For mitochondrial inherited Leigh syndrome, the correlation between severity and heteroplasmy level remains elusive.[8,9]

Here, we present 3 unrelated patients with homoplasmic or near homoplasmic m.8344A>G mutations initially presenting with MERRF syndrome who precipitously developed clinical and radiographic findings consistent with Leigh syndrome with marked brainstem features of bulbar palsy and respiratory failure following respiratory infection.

Cases

Case 1

The patient was diagnosed with MERRF at age 3 years after presenting with motor delays, sensorineural hearing loss, myoclonus, and lactic acidosis (4 millimolar). She was never found to have subcutaneous lipomas. MRI brain showed mild signal abnormalities of the insula on T2 weighted images. Blood testing showed a near homoplasmic m.8344A>G mutation.

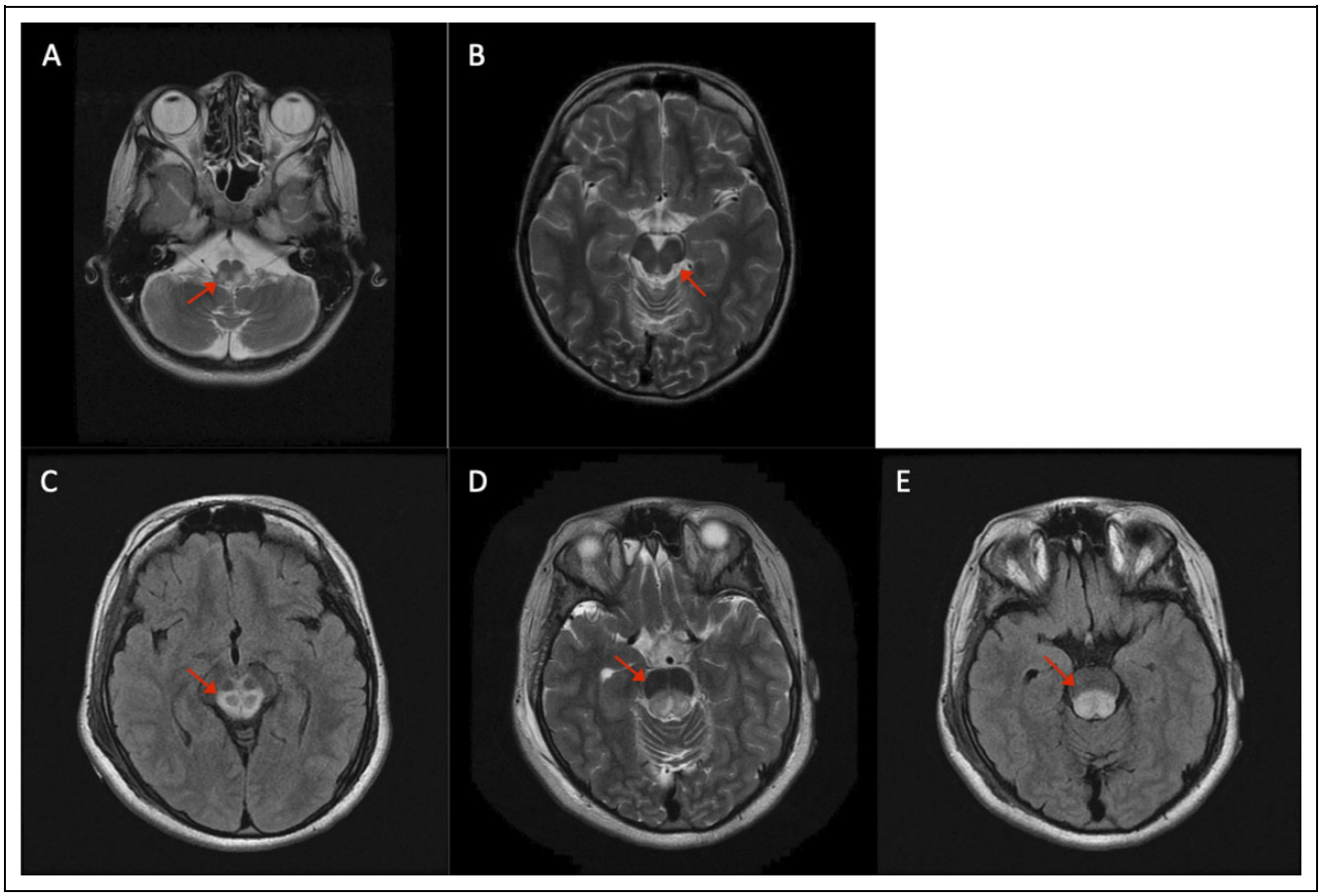

Figure 2. Case 2. At initial presentation, at age 10, MRI brain demonstrated symmetric T2 hyperintensities in the (A) medulla and (B) pons. Subsequent imaging at age 12 showed progression of the lesions in the (C) tectum, oculomotor nuclei, and cerebral peduncles as well as in the (D and E) pons and superior cerebellar peduncles.

For the next 5 years, myoclonus was relatively well-controlled on levetiracetam and clonazepam. She was able to ambulate with a walker and spoke in full sentence, but at age 7 years developed increasing tremors that impeded self-feeding and schoolwork. MRI brain (Figure 1) at that time revealed a T2 hyperintense lesion of the left medial thalamus. At age 8 years, she developed acute respiratory decompensation following 3 days of cough and rhinorrhea. She was admitted to an intensive care unit where she was found to be febrile. Coronavirus and Rhinovirus were positive and chest X-ray was concerning for aspiration pneumonia. Serum lactate ranged from 5.7-7.0 millimolar. She required intubation and supplemental oxygen. After a protracted ICU course, she was discharged to inpatient rehabilitation on CPAP; however, she was readmitted a few weeks later at which time tracheostomy was placed. She remained on mechanical ventilation at night for several years, ultimately requiring continuous mechanical ventilation by age 11 years.

From 11 to 14 years, insidious decline in cranial nerve function was noted leading to ophthalmoparesis and weakness of the muscles of mastication. Her myoclonus became increasingly refractory with worsening of her EEG background. MRI brain (Figure 1) at age 14 years revealed bilateral, symmetric T2-hyperintensities of the putamina, dorsomedial thalami, dentate nuclei, brainstem nuclei, peri-aqueductal gray matter, and central gray matter of the cervical and thoracic spinal cord. At the time of this writing, she remains gastrostomy tube, ventilator-dependent, and minimally responsive.

Case 2

The patient presented at 10 years of age with a 3-year history of tremors and unsteady gait followed by progressive weakness and voice changes. At presentation she had a 2 week history of intractable hiccups, dysphagia, dyspnea, and difficulty managing salivary secretions. On exam she was cognitively intact with hypertelorism, frontal bossing, vertical ophthalmoplegia, generalized weakness (proximal greater than distal), athetoid movements of the fingers, areflexia, truncal ataxia, dysmetria, lower extremity atrophy, and ataxic gait. Lactate was elevated in both serum (1.5-7.8 mMol/L) and CSF (3.2 mMol/L). MRI brain showed edema in the pons, medulla, and superior cerebellar peduncles (Figure 2). MRI spine was normal. EMG/NCS demonstrated a sensory axonal neuropathy. Muscle biopsy

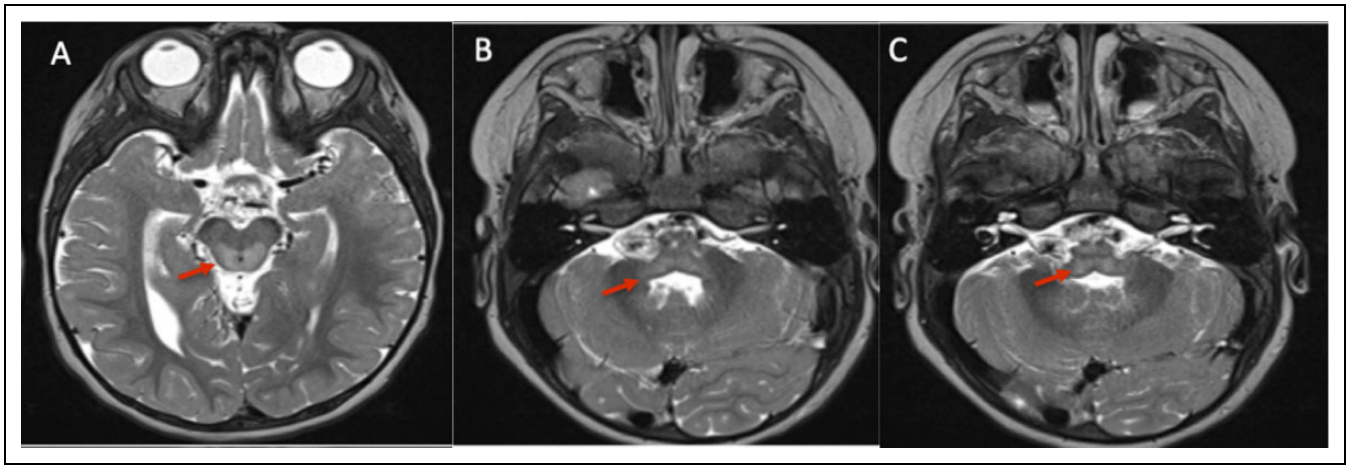

Figure 3. Case 3. Nearly symmetric T2 hyperintensities in the (A) midbrain, (B) cerebellum/cerebellar peduncles, and (C) medulla.

revealed type I fiber predominance with normal spectrophotometeric analysis. Mitochondrial genome sequencing of the skeletal muscle revealed a 97% heteroplasmic m.8344A>G mutation.

The patient decompensated acutely requiring emergent intubation for acute cardiopulmonary failure. She ultimately required placement of a tracheostomy. Over the next year, however, she showed remarkable improvement with rehabilitation. She was ambulating independently, able to ride a bicycle, her ophthalmoplegia resolved, and her tracheostomy was decannulated about 1 year from placement. Brain MRI (Figure 2) showed improvement of the previously noted signal changes with the addition of lipodystrophic changes in the neck.

One year after presentation she developed seizures that were relatively well-controlled with levetiracetam. Two years after initial presentation, at age 12 years, she developed respiratory distress and high fever (108F). Repeat MRI brain (Figure 2) showed progression of the demyelination involving the thalami, midbrain, and brainstem. She died in home hospice 2 weeks later.

Case 3

The patient presented at 17 months with acute ataxia and spells of head drops, eye flutters, tremulousness and falling in the setting of influenza A. She had a witnessed seizure in the Emergency Room. Her MRI brain and EEG at that time were normal. She returned to the hospital 2 weeks later due to return of tremors and head drops after interval improvement. She had metabolic screening labs which revealed elevated lactate and alanine (Lactate (Whole Blood): 3.0 (0.5–1.6 mmol/L) and Alanine (Plasma) 664.7 (89–440 umol/L)).

Her exam revealed a left esotropia, mildly diffuse central hypotonia, tremor with central titubation, falling, and episodes of head drop with eye flutter that had positive correlation on EEG consistent with generalized seizures. Repeat MRI brain (Figure 3) was abnormal for patchy and confluent, nearly symmetric T2 hyperintensity throughout the brainstem. She developed dysphagia followed by respiratory failure and required a tracheostomy, became ventilator dependent.

Her family history is positive for known MERRF on the maternal side, and familial targeted testing revealed m.8344A>G mutation at 97% heteroplasmy in her blood. Her asymptomatic mother has 80% heteroplasmy in blood. Her GDF-15 level is 1364. She has been stable for the past year, making interval developmental progress.

Discussion

Pleiotropy of genetic lesions in mitochondrial disease is a well-known phenomenon, however, concurrent or serial presentations of multiple syndromic phenotypes in the same individual are less common. Here, we describe 3 patients with near homoplasmic m.8344A>G mutations and early courses consistent with MERRF. All displayed the classic phenotype of myoclonus, myopathy, and/or ataxia known to occur at varying levels of heteroplasmy with the m.8344A>G genotype; however, each evolved to a phenotype consistent with Leigh syndrome. Early neuroimaging of our patients demonstrated lesions in the midline structures of the brain: the thalamus, midbrain, and pons with elevated lactate. Clinically, the patients showed features of bulbar palsy, loss of autonomic control, respiratory failure, and progressive decline in arousal. *Together with those previously published (see Table 1), our cases suggest that homoplasmic or near-homoplasmic m.8344A>G genotypes can produce a Leigh syndrome phenotype.*

The reporting of this phenotype in individuals of diverse ancestry argues against a haplotype specific phenomenon in favor of a heteroplasmy-dependent phenotype, or common end pathologic process. Further research will be required to understand the mechanism by which this homoplasmic and near homoplasmic m.8344A>G mutation produces Leigh syndrome and to better understand this phenotype among the diverse genetic lesions that result in Leigh Syndrome. Most importantly, awareness of this phenotype is essential for all providers

Table 1. Summary of Literature Review.

Citation	Heteroplasmy	Sex	Myoclonus	Muscle biopsy	Dysautonomia	Lipodystrophy	Initial MRI	Repeat MRI	Leigh syndrome lesions on histopathology	Age at initiation of mechanical ventilation	Survival following intubation	Age at death
Case 1	Near 100%	F	Yes	Not performed	No	Yes	Mild T2 signal abnormalities of the insula	Symmetric T2 hyperintensities of the putamina, thalami, dentate nuclei, brainstem nuclei, PAG, and central gray matter of cervical and thoracic spinal cord	Not performed	8 years	N/A	N/A
Case 2	97% skeletal muscle	F	Yes	Non-specific changes	Yes	Yes	Symmetric T2 hyperintensities in medulla and pons.	Progression of lesions in the tectum, oculomotor nuclei, and cerebral peduncles, pons, and superior cerebellar peduncles	Not performed	10 years	2 years	12 years
Case 3	97% blood	F	No	Not performed	Yes	No	Normal	Symmetric T2 hyperintensities throughout the brainstem	Not performed	17 months	N/A	N/A
Silvestre et al., 1993[15]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sweeney et al., 1994[16]	81% blood	M	Yes	RRF	Yes	NR	T2 hyperintense lesion of posterior brainstem from dorsal column nuclei to midbrain	Spread of prior lesion to include thalamus	Subthalamic region, brainstem	18 years	7 weeks	18 years
Howell et al., 1996[11]	unknown	M	Yes	Non-specific changes	Yes	NR	n/a	n/a	Basal ganglia, brainstem	Not reported	NR	4 months
Monden et al., 2013[13]	99% skeletal muscle	M	Yes	Not performed	Yes	NR	Diffuse cortical atrophy	T2 hyperintense lesions of the pons, medulla	NR	6 years	NR	NR

(continued)

Table 1. (continued)

Citation	Heteroplasmy	Sex	Myoclonus	Muscle biopsy	Dysautonomia	Lipodystrophy	Initial MRI	Repeat MRI	Leigh syndrome lesions on histopathology	Age at initiation of mechanical ventilation	Survival following intubation	Age at death
Shen et al., 2018[14]	95% blood	M	Yes	RBF on SDH staining	Yes	NR	T2 hyperintense lesions of hypothalamic, PAG, midbrain and medullary tegmentum	Prior T2 hyperintense lesions and thalami	NR	16 years	2 years	18 years
Orcesi et al., 2006[10]	75%	M	Yes	No myopathic changes	NR	NR	Left cerebellar hemisphere hypoplasia, otherwise no signal changes	Symmetric T2 hyperintensities in putamen	NR	N/A at age 8 years, 9 months	N/A	N/A
Ito et al., 2008[12]	NR	M F M	Yes NR Yes	NR	NR	NR	Nonspecific volume loss; Symmetric T2 hyperintensities in midbrain around PAG. Atrophy of midbrain, pons, MCP, and cerebellum. Atrophy of cerebellum and SCP.	Bilateral T2 hyperintensities around PAG. Atrophy of midbrain, pons, MCP, cerebellum, and SCP Not reported Not reported	NR	NR	NR	NR

NR: Not reported; PAG: Peri-aqueductal gray matter; SCP: Superior cerebellar peduncles; MCP: Middle cerebellar peduncles.

counseling patients on the implications of a homoplasmic or near homoplasmic m.8344A>G mutation diagnosis.

Conclusion

Individuals homoplasmic or near-homoplasmic for m.8344A>G may present with classic symptoms of MERRF, yet evolve to Leigh syndrome over time, possibly in the setting of an infectious or respiratory trigger. This distinct phenotype has important clinical implications in that prognosis is different and management requires a different approach. Recognition of the association of the m.8344A>G mutation with an early MERRF phenotype that transitions to Leigh syndrome will allow for appropriate anticipatory guidance in the care of these patients.

Author Contributions

SNR, MKK, and MW substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data; drafted the manuscript; and critically revised the manuscript for important intellectual content. AG and AK substantially contributed to conception or design; contributed to acquisition, analysis, or interpretation of data. All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

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ORCID iD

Sam Nicholas Russo, MD https://orcid.org/0000-0001-5045-9301

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