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CLINICAL CASE REPORT

Rod bipolar cell dysfunction in *POLG* retinopathy

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Abstract
Objective To report the clinical and novel electrophysiological features in a child with *POLG*-related sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO).
Methods The proband, a male child of Indian descent, underwent serial systemic and ophthalmological evaluations from birth until 14 years of age. Eye examinations included visual acuity and extraocular movement assessments, fundus photography, spectral domain optical coherence tomography and full-field electroretinography (ERG). Detailed genetic testing was also performed.
Results The child carried a homozygous mutation in *POLG* (c.911T > G/p.Leu304Arg) and manifested systemic features such as seizures, headaches, areflexia, hypotonia, myopathy and vomiting. The child's distance visual acuity was 0.50 and 0.40 LogMAR in the right and left eyes, respectively. Bilateral ophthalmoplegia and ptosis were observed at 5 years of age. The dark-adapted (DA) ERG responses to 2.29 cd s m^{-2} and 7.6 cd s m^{-2} stimuli showed a markedly reduced *b*/*a* ratio; an electronegative configuration was noted to a DA 7.6 ERG.
Conclusion This is the first documented case of an electronegative ERG in a *POLG*-related disorder consistent with generalized rod ON-bipolar dysfunction. The rest of the proband's systemic and ophthalmological features were consistent with SANDO but some features overlapped with other *POLG*-related disorders such as Alpers–Huttenlocher syndrome and autosomal dominant progressive external ophthalmoplegia demonstrating the wide phenotypic overlap expected due to *POLG* mutations.

Keywords POLG · POLG1 · Polymerase gamma · Electroretinography · Light signal transduction · Retinal bipolar cells

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Introduction

POLG (*POLG1*) is a nuclear gene that codes for the catalytic subunit of polymerase γ, an enzyme with both polymerase and exonuclease functions, allowing for the proofreading of mitochondrial DNA (mtDNA) [1]. Damaging mutations in *POLG* could lead to defective polymerase or exonuclease activity of the

enzyme, thereby causing mtDNA mutations. Point mutations in mtDNA arise from defective polymerase activity of the *POLG* enzyme, whereas defective exonuclease activity results in an accumulation of both point mutations and deletions in the mtDNA [1–6].

Mutations in *POLG* are known to cause a range of autosomal dominant (AD) and autosomal recessive (AR) disorders with overlapping clinical features including seizure, developmental delay, migraines, stroke-like episodes, extrapyramidal movement disorders, peripheral neuropathy, ataxia, depression, anxiety, sensorineural hearing loss, retinopathy, cataracts, gastrointestinal dysmotility, liver failure, myopathy, hypotonia, diabetes mellitus, primary ovarian/testicular failure and cardiomyopathies [2, 6–10]. Despite the overlapping features, there are distinct clinical phenotypes described due to *POLG* mutations which include childhood myocerebrohepatopathy spectrum (CMS; AR), myoclonic epilepsy myopathy sensory ataxia (MEMSA; AR), sensory ataxic neuropathy, dysarthria and ophthalmoparesis [SANDO; AR; also known as ataxia neuropathy spectrum (ANS)], autosomal recessive and dominant progressive external ophthalmoplegia (PEO) and the most severe form Alpers–Huttenlocher syndrome (AHS; AR) [6, 7].

CMS is characterized by infantile onset of its cardinal features which include hypotonia, developmental delay, hepatopathy and GI involvement [6]. The classical tetrad of MEMSA includes seizures, myopathy, neuropathy and ataxia in the absence of ophthalmoplegia [7]. The characteristic features associated with SANDO (ANS) are ataxia and neuropathy with many developing seizures and ophthalmoplegia [7]**.** AD PEO is characterized by migraines, ophthalmoplegia and CNS involvement, while the AR PEO is associated with ophthalmoplegia, weakness and the potential for cardiac and gastrointestinal symptoms [6, 11–13]. Hallmark features of AHS include developmental delay, hepatopathy, seizures and GI involvement [6, 14–16]. A number of overlapping ocular features have been associated with these clinical entities, including external ophthalmoplegia, pigmentary retinopathy, cataracts and eyelid ptosis [9, 17, 18].

Regardless of etiology, acquired or inherited, many generalized retinal disorders require a full-field electroretinogram (ERG) for an accurate diagnosis and prognosis [19]. While some conditions may have hallmark signs visible on fundus examination, some disorders have normal retinal appearance and are better assessed and diagnosed with an ERG [19]. In cases with generalized trans-synaptic or bipolar cell deficits, an electronegative configuration to dark-adapted (DA) bright flash (DA 3.0 and DA 10.0) ERGs is seen, as the b-wave amplitude is smaller than the a-wave amplitude [19]. An electronegative ERG is characteristic of retinal disorders such as congenital stationary night blindness (CSNB), X-linked retinoschisis and juvenile Batten disease [19].

POLG is ubiquitously expressed, and in the retina, it is expressed in the inner and outer plexiform layers as well as the ganglion cells [1]. Neuron-specific mice models of *POLG* with impaired exonuclease activity showed a reduced *b*:*a* ratio of the scotopic ERG suggesting retinal rod ON-bipolar dysfunction [1]. A normal ERG is one of the minor diagnostic criteria for AHS [20]; however, there are only a few cases in the literature that have reported on ERG findings [21]. This is a case report of a boy with biallelic *POLG* mutations, demonstrating the first documented occurrence of an electronegative ERG in addition to typical systemic features of a *POLG*-related disorder.

Case report

The study was approved by the Research Ethics Board at the Hospital for Sick Children Toronto, and informed consent was obtained from the parent; the study protocols adhered to the tenets of the Declara-tion of Helsinki.

Systemic features

The proband is of Indian descent, and there was no known history of hereditary illnesses. After an uneventful pregnancy, the proband was born at term via spontaneous vaginal delivery. Growth parameters for height and weight were in the third percentile. Upon weaning at 6 months and introduction of solid foods, the child was noted to have a decreased appetite with episodes of cyclical vomiting. The child began to walk at 9 months and speak sentences after 2 years. The child displayed no signs of dysarthria or receptive/expressive language deficits and there was no regression of language skills. After a series of afebrile seizures, at 2 years, the child was started on anticonvulsant therapy (oxcarbazepine). Following two

seizure-free years, oxcarbazepine was discontinued and there were no recurrences.

At the age of four, the child developed worsening anorexia and a mild limitation of gross motor activities. Coenzyme Q10, creatine, alpha lipoic acid and carnitine were sequentially added from the age of 9 years in an attempt to slow the dystrophic pattern. At 11 years of age, weakness of his respiratory muscles was noted resulting in mild obstructive sleep apnea, a chronic cough and the requirement of a cough assistance device.

By the age of twelve, the child had to be fed through a G-tube due to the dysphagia, was wheelchair bound and needed assistance with all aspects of self-care. At 13, the child was hospitalized for aspiration pneumonia that required extensive use of the cough assistance device and salivary Botox to control his secretions. The child also developed bilateral hand contractures, and at his most recent visit, at 14, he is failing to thrive, and palliative care is likely the only treatment option.

Ocular features

At the age of five, the child had symptoms of photophobia and on evaluation, bilateral ptosis was noted alongside a difficulty with extraocular eye movements. At 9 years, the palpebral fissure was 4 mm on the right and 7 mm on the left, requiring extension of the neck to maintain eye contact. Extraocular movements showed elevation (− 3), abduction (− 1) and adduction (− 1) deficits in either eye. The child's uncorrected and corrected visual acuity was 0.50 and 0.40 LogMAR in the right and left eyes, respectively. The cycloplegic refraction was + 3.00 and + 1.50/− 3.00 × 180° in the right and left eyes, respectively. Fundus evaluation was normal, and the spectral domain optical coherence tomography (SD-OCT; Bioptigen, Inc) showed normal central retinal thickness and layering (Fig. 1). Full-field ERG was performed on Espion (Diagnosys LCC, Lowell, MA) system using ERG-Jet contact lens electrodes. Due to patient fatigue (myopathy) and other health considerations, the ERG was performed monocularly over two sessions; the right eye scotopic and photopic ERGs were performed at 10 and 13 years, respectively, and the left eye ERG was performed at 13 years. Hence, some steps of the scotopic ERG were in compliance with an earlier ISCEV standard, whereas the remainder of the steps were in compliance with latest ISCEV standards [22, 23]. The dark-adapted (DA) dim-light ERG (DA 0.01) showed low normal *b*-wave amplitude; DA 2.29 and DA 7.6 ERG's showed normal *a*-wave amplitudes and reduced *b*/*a* ratio. The DA 7.6 ERGs showed an electronegative configuration. The light-adapted ERGs (LA 3.0 30 Hz and LA 3.0 2 Hz) were within normal limits; cone ON–OFF ERGs performed using white stimulus (166.66 cd m^{-2}) on white background (30 cd m^{-2}) and an amber stimulus on a green background [19] were normal (Fig. 2).

Genetic results

At the age of ten, a previously reported homozygous missense mutation was identified in *POLG* (c.911T > G/p.Leu304Arg). The child was also screened for CSNB using a next-generation sequencing panel containing 18 known genes; no pathogenic variants or copy number variations were identified.

Discussion

This is the first documented case of an electronegative ERG, suggestive of generalized rod ON-bipolar dysfunction, in a *POLG*-related disorder. The proband presented with well-documented systemic and ocular features associated with *POLG*-related disorders including seizures, headaches, areflexia, hypotonia, myopathy, vomiting, ophthalmoplegia and ptosis; his clinical phenotype was most consistent with SANDO (Table 1). Typically, SANDO presents later in life with ataxia as the principal feature (average age: 32.9 years; range 5–73 years) followed by PEO within a decade; dysarthria and seizures are relatively uncommon [24]. Although the proband shared six clinical features with AHS, the presence of myopathy and lack of liver involvement suggest his phenotype to be SANDO [7], acknowledging that the severity and earlier presentation of symptoms in the proband place him along a continuum of clinical presentations seen in SANDO. The phenotypic descriptions of various *POLG*-related disorders, with their hallmark signs and symptoms, and inheritance patterns are summarized in Table 1.

With the wide variability of onset and severity in *POLG*-related disorders, it can be difficult to predict and compare phenotypes. For example, seizure is a

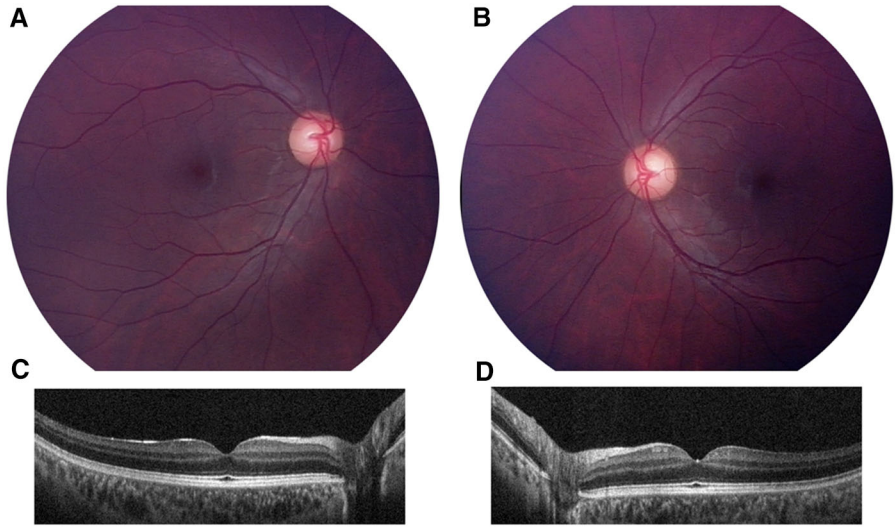

Fig. 1 Fundus and spectral domain optical coherence tomography (SD-OCT) from the proband. **A** and **B** show normal fundus photographs from the right and left eyes, respectively. **C** and **D** show horizon line scan of the SD-OCT through the fovea that demonstrates normal central retinal layering in either eye

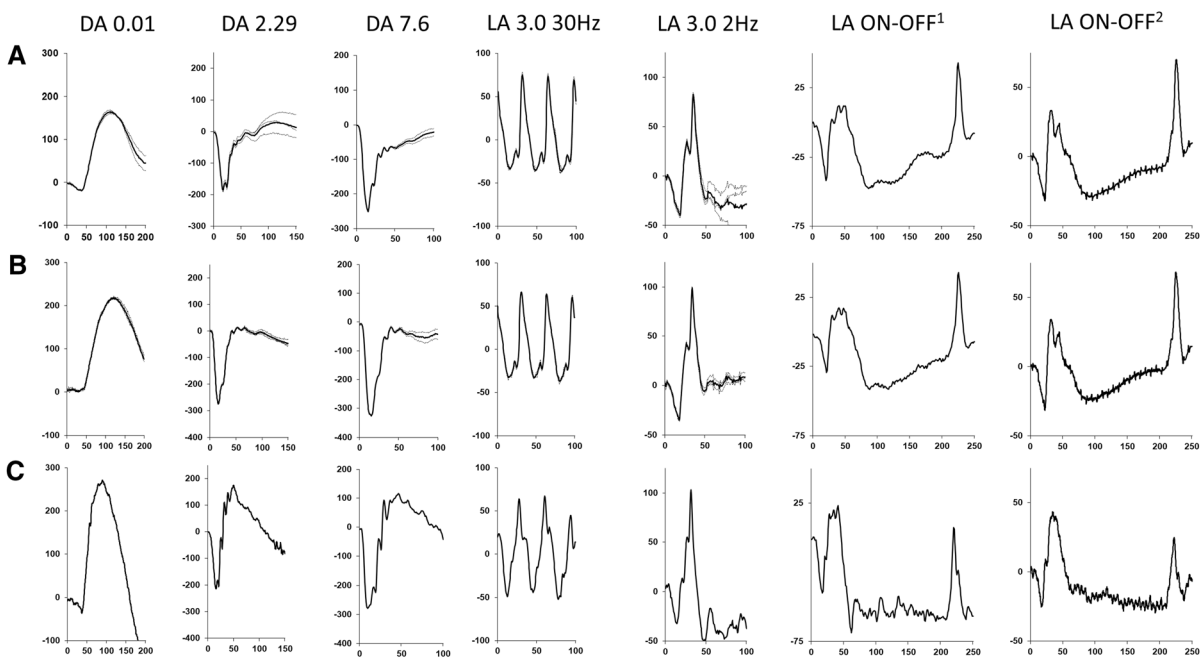

Fig. 2 Full-field ERG results from the proband (**A** right eye and **B** left eye). Dim-light scotopic ERG (DA 0.01) shows a low normal b-wave amplitude; DA 2.29 and DA 7.6 ERGs show normal a-wave amplitude and markedly reduced b-wave amplitude; DA 7.6 ERGs showed an electronegative configuration. The light-adapted 30 Hz flicker ERG showed normal amplitudes [109 and 99 μV in the right and left eyes, respectively; (normal range 64–192 μV); median-112 μV] and implicit times [31 ms in either eye; (normal range: 27–36 ms)]. The LA 3.0 2 Hz showed normal a-wave amplitudes [40 and 35 μV in the right and left eyes, respectively; (normal range 19–72 μV)]; b-wave amplitudes [123 and 134 μV in the right and left eyes, respectively; (normal range 84–255 μV; median-133 μV)] and implicit times [34 ms in either eye; (normal range 32–39 ms; median-33 ms)] were normal. The cone ON–OFF ERGs to a white stimulus on a white background (LA ON-OFF^1) and an amber stimulus to a green background (LA ON-OFF^2) were normal. **c** Full-field ERG from a control subject

Table 1 Phenotypic range and systemic involvement in *POLG*-related disorders

POLG-related disease	AHS	CMS	MEMSA	SANDO/ ANS	ARPEO	ADPEO	Proband
Seizures	++ (16)	+ (25)	++ (7, 26)	++ (27, 29)	− (11–13)	+ (28)	**Present**
Headaches	+ (17, 30)	–	–	+ (27)	− (11–13)	++ (6)	**Present**
Stroke/stroke-like episodes	+ (43)	–	–	–	− (11–13)	–	Absent
Movement disorders	+ (43)	–	–	+ (10, 31)	− (11–13)	–	Absent
Parkinsonism	+ (9)	–	–	–	− (11–13)	+ (9, 32)	Absent
Neuropathy and ataxia	+ (7)	–	++ (7)	++ (27, 29)	− (11–13)	+ (9, 32)	Could not be assessed
Areflexia and hypotonia	+ (7)	++ (31)	–	+ (27)	− (11–13)	–	**Present**
Episodic psychomotor regression	+ (7, 14)	–	–	–	− (11–13)	–	Absent
Loss of cognitive function	+ (7)	–	–	+ (10)	− (11–13)	–	Absent
Cortical visual loss	+ (17, 43)	–	–	− (31)	− (11–13)	–	Absent
Liver involvement	++ (7, 14)	++ (25)	–	+ (31)	− (11–13)	–	Absent
Developmental delay	++ (15)	++ (25)	–	+ (31)	− (11–13)	–	Absent
Lactic acidosis	+ (14)	+ (25)	–	+ (10)	− (11–13)	-	Absent
Myopathy	–	+ (25)	++ (7)	+ (29)	+ (6, 11–13)	+ (9, 32)	**Present**
Pancreatitis	+ (15)	+ (25)	–	–	− (11–13)	–	Absent
Renal tubular acidosis	–	+ (25)	–	–	− (11–13)	–	Absent
Vomiting	+ (31)	+ (25)	–	–	− (11–13)	–	**Present**
Hearing loss	–	+ (25)	–	+ (29, 31)	− (11–13)	+ (9, 32)	Absent
Ophthalmoplegia	+ (14)	–	− (7)	++ (27)	++ (11–13)	++ (32)	**Present**
Ptosis	–	–	–	–	+ (11–13)	+ (11)	**Present**
Strabismus	–	–	–	–	(11–13)	+ (11)	Absent
Depression	–	–	–	+ (27)	− (11–13)	+ (9, 32)	Absent
Hypogonadism	–	–	–	–	− (11–13)	+ (9, 32)	Absent
Cataracts	–	–	–	–	− (11–13)	+ (9, 32)	Absent
Cardiomyopathy	+ (14)	–	–	+ (10)	+ (6, 11–13)	+ (7)	Absent
Gastrointestinal dysmotility	++ (14)	++ (31)	–	+ (10)	+ (6, 11–13)	+ (7)	**Present**

A referenced "+" or "−" symbol indicates a literary source reporting the presence or absence of a sign as a key feature of a disorder and "++" represents a hallmark feature of a syndrome, whereas an unreferenced "–" symbol indicates a lack of reported evidence

AHS Alpers–Huttenlocher syndrome, *CMS* childhood myocerebrohepatopathy spectrum, *MEMSA* myoclonic epilepsy myopathy sensory ataxia, *SANDO/ANS* sensory ataxic neuropathy, dysarthria and ophthalmoparesis/ataxia neuropathy spectrum, *ARPEO* autosomal recessive progressive external ophthalmoplegia, *ADPEO* autosomal dominant progressive external ophthalmoplegia

fairly common and overlapping feature in most *POLG*-related disorders (Table 1). The literature often describes treatment-resistant seizures as a symptom that develops later in the disease progression [25–29]; however, Tzoulis et al. reported epilepsy as the presenting complaint in half of their *POLG* cohort [30]. In SANDO, the prevalence of seizure was observed in 29% of cases at presentation [24]. In the present report, the proband developed seizures at the age of two, rather early in the course of the disease, and is on remission following treatment. The proband also reported sporadic headaches, beginning at the age of four, while Tzoulis et al. documented headaches as the presenting complaint in over 25% of cases [30]. Specifically in ANS, headaches have been documented to precede other symptoms by many years [7]. From the age of four, the proband had hypotonia in all four extremities, and the examiner's reports indicated difficulty eliciting tendon reflexes throughout the child's life. Patients with AHS and CMS also have reported hypotonia and areflexia, often presenting in the first 2 or 3 years of life, while these symptoms have yet to be reported in SANDO or ANS [7, 31]. The proband suffered from early vomiting, which has been

similarly described in patients with AHS and CMS; dysphagia is noted on presentation in 24% of molecularly confirmed cases of SANDO/ANS [24, 25, 31].

Myopathy is a fairly ubiquitous symptom of *POLG*-related disorders, having its onset described anywhere from 3 to 60 years of age, with variability in its severity and pace of progression [25]. Within SANDO/ANS, roughly 25% of cases have documented cramps, but a recent report estimated that 52% of cases with *POLG*-related SANDO had limb girdle paresis [7, 24, 25]. The proband had symptoms of severe progressive myopathy documented as early as the age of four. Ocular myopathic signs such as ptosis and external ophthalmoplegia are common in most *POLG*-related disorders with the age of onset ranging from 10 years of age to adulthood; these symptoms were first noted in the proband at the age of 5 years [11–13, 32]. Ophthalmoplegia has been documented in up to half of SANDO/ANS patients; however, some report extraocular muscle involvement as both a later and a milder symptom, relative to the sensory ataxic neuropathy [7, 73]. Hanisch et al. reported that among molecularly confirmed SANDO, ataxia was the commonest disabling symptom at presentation (67%) [24]. The absence of frank ataxia even at the time of the most recent examination was due to the proband's limited capacity for movement.

While the proband displays many similarities to other known *POLG* phenotypes, his ocular phenotype is distinct in the fact that he had an electronegative ERG, under dark-adapted conditions, consistent with rod ON-bipolar cell dysfunction. The cone ON and OFF bipolar functions were normal. In the literature, patients with *POLG* mutations-related AHS are often described as having normal ERGs [20, 21]; the relative paucity of reported ERG abnormalities in the literature may be in part due to infrequent testing in this patient population. Polg has been shown to be well expressed in the mice inner retina, and mutant mice with defective exonuclease activity have features of retinal ON-bipolar dysfunction on ERG testing [1]. The sparing of cone ON and OFF systems in the proband is striking as most inherited conditions with selective inner retinal dysfunction affect both rod and cone bipolar systems, with the exception of Duchenne/Becker muscular dystrophy, the findings of which are similar to what is noted in the proband [19, 33]. Fundus examination was normal in the proband; however, reported findings in *POLG*-related disorders range from normal retinal examination to pigmentary retinopathy [9, 11]. It is notable that the proband had symptoms of photophobia, the cause for which is unknown.

POLG-related disorders are genetically heterogeneous, and there are over 100 mutations associated with AHS, over 80 mutations associated with PEO and over 25 mutations associated with SANDO-related syndromes [34]. The p.Leu304Arg variant found in the proband has been reported in the literature in both homozygous and compound heterozygous state numerous times. The p.Leu304Arg variant in homozygous state has almost always been associated with SANDO/ANS disease spectrum in the literature, with an age of onset between 2 and 23 years of age [35–38]. The p.Leu304Arg variant in compound heterozygous state with other variants led to a range of phenotypic presentations [36]. For instance, Van Goethem et al. described a sibship with compound heterozygous mutations (p.Leu304Arg/Ala467Thr) whose symptoms of PEO and skeletal muscle weakness (red ragged fibers on muscle biopsy) had a mean age of onset of 25 ± 7 years, with no retinal or hepatic involvement [11], whereas Stewart et al. described a patient with the same variants (p.Leu304Arg/Ala467Thr) who had seizures, peripheral neuropathy and hepatopathy consistent with AHS [39]. Further, both missense and frameshifting variants in trans with the p.Leu304Arg variant have been associated with AHS [40, 41]. Other missense variants in combination with the p.Leu304Arg allele have been associated with SANDO and AR PEO, respectively [38, 42]. This is consistent with the existing literature wherein there is only limited genotype–phenotype associations with *POLG* variants (as seen in p.Leu304Arg homozygous cases) [34, 43].

Conclusion

This is a case of a young boy, who carried homozygous *POLG* mutations and demonstrated a series of symptoms associated with a broad category of *POLG* syndromes including seizures, headaches, areflexia/hypotonia, myopathy, vomiting, ophthalmoplegia and ptosis. His features were most consistent with SANDO; however, the proband also demonstrated selective rod ON-bipolar cell dysfunction, a feature never previously reported in human *POLG*-related

disorders. However, the role of *POLG* in retinal signaling is unknown and needs to be further studied.

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Compliance with ethical standards

Statement of human rights The study was approved by the Research Ethics Board at the Hospital for Sick Children Toronto. The study protocols adhered to the tenets of the Declaration of Helsinki.

Statement on the welfare of animals The study involved no research on animals.

Informed consent Parental informed consent was obtained for the study.

Conflict of interest No conflicting relationships exist for any author.

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