Rod bipolar cell dysfunction in *POLG* retinopathy

Kit Green Sanderson . Eoghan Millar . Anupreet Tumber . Regan Klatt .

Neal Sondheimer . Ajoy Vincent

Received: 21 April 2020 / Accepted: 9 June 2020 / Published online: 21 June 2020

© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract

CLINICAL CASE REPORT



<https://doi.org/10.1007/s10633-020-09777-w>

*Objective* To report the clinical and novel electro- physiological features in a child with *POLG*-related sensory ataxic neuropathy, dysarthria and ophthalmo- paresis (SANDO).

*Methods* The proband, a male child of Indian descent, underwent serial systemic and ophthalmo- logical evaluations from birth until 14 years of age. Eye examinations included visual acuity and extraoc- ular 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, are- flexia, 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

K. G. Sanderson · N. Sondheimer · A. Vincent Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

E. Millar · A. Tumber · R. Klatt · A. Vincent (&) Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, University of Toronto,

Toronto, Canada

e-mail: [ajoy.vincent@sickkids.ca](mailto:ajoy.vincent@sickkids.ca)

N. Sondheimer

Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada

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 con- figuration 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 dysfunc- tion. The rest of the proband’s systemic and ophthal- mological features were consistent with SANDO but some features overlapped with other *POLG*-related disorders such as Alpers–Huttenlocher syndrome and autosomal dominant progressive external ophthalmo- plegia demonstrating the wide phenotypic overlap expected due to *POLG* mutations.

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

Introduction

*POLG* (*POLG1*) is a nuclear gene that codes for the catalytic subunit of polymerase c, an enzyme with both polymerase and exonuclease functions, allowing for the proofreading of mitochondrial DNA (mtDNA) [[1](#_bookmark8)]. 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](#_bookmark8)–[6](#_bookmark14)].

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 dis- orders, peripheral neuropathy, ataxia, depression, anxiety, sensorineural hearing loss, retinopathy, catar- acts, gastrointestinal dysmotility, liver failure, myopa- thy, hypotonia, diabetes mellitus, primary ovarian/ testicular failure and cardiomyopathies [[2](#_bookmark10), [6](#_bookmark14)–[10](#_bookmark4)]. 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 neu- ropathy, dysarthria and ophthalmoparesis [SANDO; AR; also known as ataxia neuropathy spectrum (ANS)], autosomal recessive and dominant progres- sive external ophthalmoplegia (PEO) and the most severe form Alpers–Huttenlocher syndrome (AHS; AR) [[6](#_bookmark14), [7](#_bookmark17)].

CMS is characterized by infantile onset of its cardinal features which include hypotonia, develop- mental delay, hepatopathy and GI involvement [[6](#_bookmark14)]. The classical tetrad of MEMSA includes seizures, myopathy, neuropathy and ataxia in the absence of ophthalmoplegia [[7](#_bookmark17)]. The characteristic features asso- ciated with SANDO (ANS) are ataxia and neuropathy with many developing seizures and ophthalmoplegia [[7](#_bookmark17)]. AD PEO is characterized by migraines, ophthal- moplegia and CNS involvement, while the AR PEO is associated with ophthalmoplegia, weakness and the potential for cardiac and gastrointestinal symptoms [[6](#_bookmark14), [11](#_bookmark5)–[13](#_bookmark6)]. Hallmark features of AHS include devel- opmental delay, hepatopathy, seizures and GI involve- ment [[6](#_bookmark14), [14](#_bookmark7)–[16](#_bookmark9)]. A number of overlapping ocular features have been associated with these clinical entities, including external ophthalmoplegia, pigmen- tary retinopathy, cataracts and eyelid ptosis [[9](#_bookmark3), [17](#_bookmark11), [18](#_bookmark12)]. Regardless of etiology, acquired or inherited, many generalized retinal disorders require a full-field elec- troretinogram (ERG) for an accurate diagnosis and prognosis [[19](#_bookmark13)]. 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](#_bookmark13)]. 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](#_bookmark13)]. An electronegative ERG is characteristic of retinal disorders such as congenital stationary night blindness (CSNB), X-linked retinoschisis and juvenile Batten disease [[19](#_bookmark13)].

*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](#_bookmark8)]. 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](#_bookmark8)]. A normal ERG is one of the minor diagnostic criteria for AHS [[20](#_bookmark15)]; however, there are only a few cases in the literature that have reported on ERG findings [[21](#_bookmark16)]. This is a case report of a boy with biallelic *POLG* mutations, demonstrating the first documented occur- rence 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 recep- tive/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 anticon- vulsant 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 activ- ities. 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 pneumo- nia 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 9 180° 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](#_bookmark0)). 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, respec- tively, 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](#_bookmark18), [23](#_bookmark19)]. 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](#_bookmark13)] were normal (Fig. [2](#_bookmark1)).

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 dys- function, 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](#_bookmark2)). 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](#_bookmark21)]. 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](#_bookmark17)], 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](#_bookmark2).

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

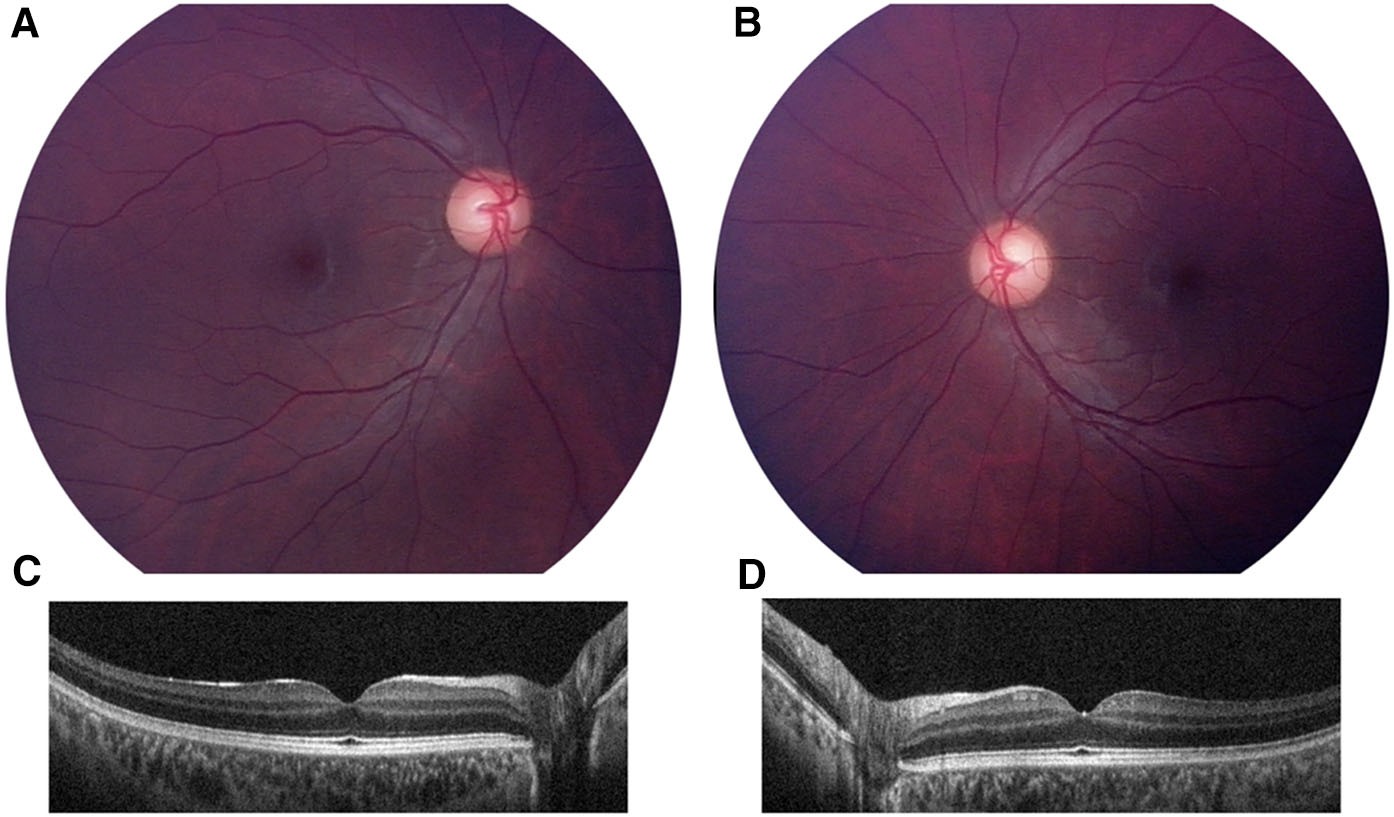


Fig. 1 Fundus and spectral domain optical coherence tomog- raphy (SD-OCT) from the proband. A and B show normal fundus photographs from the right and left eyes, respectively.

C and D show horizon line scan of the SD-OCT through the fovea that demonstrates normal central retinal layering in either eye

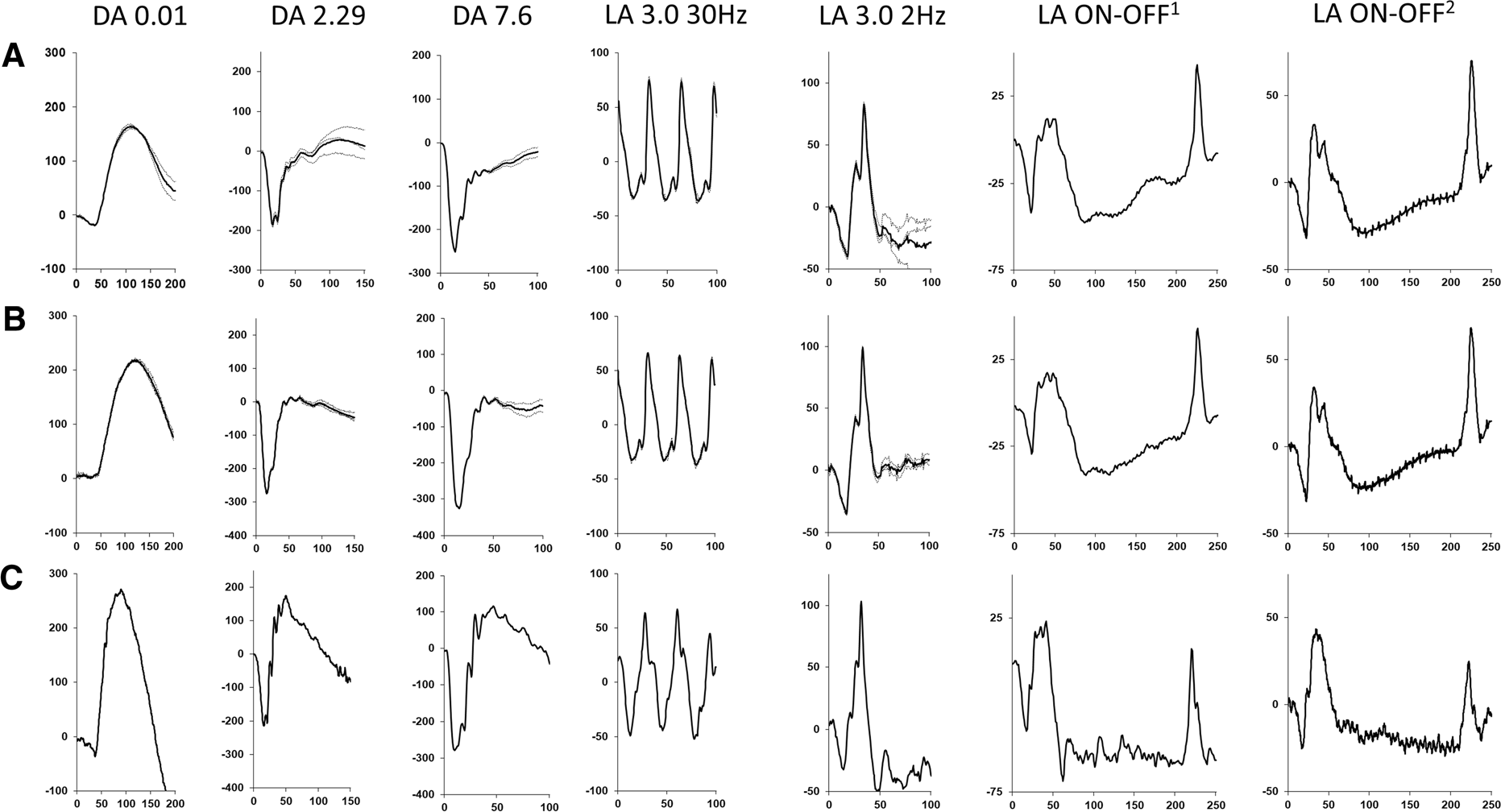


Fig. 2 Full-field ERG results from the proband (A right eye and B left eye). Dim-light scotopic ERG (DA 0.01) shows a low normal b-wave amplitude; DA 2.29 and DA 7.6 ERGs show normal a-wave amplitude and markedly reduced b-wave amplitude; DA 7.6 ERGs showed an electronegative configu- ration. The light-adapted 30 Hz flicker ERG showed normal amplitudes [109 and 99 lV in the right and left eyes, respectively; (normal range 64–192 lV); median-112 lV] 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 lV in the right and left eyes, respectively; (normal range 19–72 lV)]; b-wave amplitudes [123 and 134 lV in the right and left eyes, respectively; (normal range 84–255 lV; median- 133 lV)] 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-OFF1) and an amber stimulus to a green background (LA ON-OFF2) 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 | 11 (16) | 1 (25) | 11 (7, 26) | 11 (27, 29) | - (11–13) | 1 (28) | Present |
| Headaches | 1 (17, 30) | – | – | 1 (27) | - (11–13) | 11 (6) | Present |
| Stroke/stroke-like episodes | 1 (43) | – | – | – | - (11–13) | – | Absent |
| Movement disorders | 1 (43) | – | – | 1 (10, 31) | - (11–13) | – | Absent |
| Parkinsonism | 1 (9) | – | – | – | - (11–13) | 1 (9, 32) | Absent |
| Neuropathy and ataxia | 1 (7) | – | 11 (7) | 11 (27, 29) | - (11–13) | 1 (9, 32) | Could not be assessed |
| Areflexia and hypotonia | 1 (7) | 11 (31) | – | 1 (27) | - (11–13) | – | Present |
| Episodic psychomotor regression | 1 (7, 14) | – | – | – | - (11–13) | – | Absent |
| Loss of cognitive function | 1 (7) | – | – | 1 (10) | - (11–13) | – | Absent |
| Cortical visual loss | 1 (17, 43) | – | – | - (31) | - (11–13) | – | Absent |
| Liver involvement | 11 (7, 14) | 11 (25) | – | 1 (31) | - (11–13) | – | Absent |
| Developmental delay | 11 (15) | 11 (25) | – | 1 (31) | - (11–13) | – | Absent |
| Lactic acidosis | 1 (14) | 1 (25) | – | 1 (10) | - (11–13) | - | Absent |
| Myopathy | – | 1 (25) | 11 (7) | 1 (29) | 1 (6, 11–13) | 1 (9, 32) | Present |
| Pancreatitis | 1 (15) | 1 (25) | – | – | - (11–13) | – | Absent |
| Renal tubular acidosis | – | 1 (25) | – | – | - (11–13) | – | Absent |
| Vomiting | 1 (31) | 1 (25) | – | – | - (11–13) | – | Present |
| Hearing loss | – | 1 (25) | – | 1 (29, 31) | - (11–13) | 1 (9, 32) | Absent |
| Ophthalmoplegia | 1 (14) | – | - (7) | 11 (27) | 11 (11–13) | 11 (32) | Present |
| Ptosis | – | – | – | – | ? (11–13) | 1 (11) | Present |
| Strabismus | – | – | – | – | (11–13) | 1 (11) | Absent |
| Depression | – | – | – | 1 (27) | - (11–13) | 1 (9, 32) | Absent |
| Hypogonadism | – | – | – | – | - (11–13) | 1 (9, 32) | Absent |
| Cataracts | – | – | – | – | - (11–13) | 1 (9, 32) | Absent |
| Cardiomyopathy | 1 (14) | – | – | 1 (10) | 1 (6, 11–13) | 1 (7) | Absent |
| Gastrointestinal dysmotility | 11 (14) | 11 (31) | – | 1 (10) | 1 (6, 11–13) | 1 (7) | Present |

A referenced ‘‘1’’ or ‘‘-’’ symbol indicates a literary source reporting the presence or absence of a sign as a key feature of a disorder and ‘‘11’’ 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](#_bookmark2)). The literature often describes treatment-resistant seizures as a symptom that develops later in the disease progression [[25](#_bookmark23)–[29](#_bookmark27)]; however, Tzoulis et al. reported epilepsy as the presenting complaint in half of their *POLG* cohort [[30](#_bookmark29)]. In SANDO, the prevalence of seizure was observed in 29% of cases at presentation [[24](#_bookmark21)]. 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](#_bookmark29)]. Specifically in ANS, headaches have been docu- mented to precede other symptoms by many years [[7](#_bookmark17)]. 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](#_bookmark17), [31](#_bookmark30)]. 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 molec- ularly confirmed cases of SANDO/ANS [[24](#_bookmark21), [25](#_bookmark23), [31](#_bookmark30)]. 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](#_bookmark23)]. Within SANDO/ANS, roughly 25% of cases have docu- mented cramps, but a recent report estimated that 52% of cases with *POLG-*related SANDO had limb girdle paresis [[7](#_bookmark17), [24](#_bookmark21), [25](#_bookmark23)]. 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](#_bookmark5)–[13](#_bookmark6), [32](#_bookmark33)]. 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](#_bookmark17), [73](#_bookmark25)]. Hanisch et al. reported that among molecularly confirmed SANDO, ataxia was the com- monest disabling symptom at presentation (67%) [[24](#_bookmark21)]. 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](#_bookmark15), [21](#_bookmark16)]; 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](#_bookmark8)]. 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](#_bookmark13), [33](#_bookmark34)]. Fundus examination was normal in the proband; however, reported findings in *POLG*-related disorders

range from normal retinal examination to pigmentary retinopathy [[9](#_bookmark3), [11](#_bookmark5)]. It is notable that the proband had symptoms of photophobia, the cause for which is unknown.

*POLG*-related disorders are genetically heteroge- neous, 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](#_bookmark36)]. 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 homozy- gous 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](#_bookmark20)–[38](#_bookmark24)]. The p.Leu304Arg variant in compound heterozygous state with other variants led to a range of phenotypic presentations [[36](#_bookmark22)]. For instance, Van Goethem et al. described a sibship with compound heterozygous mutations (p.Leu304Arg/Ala467Thr) whose symp- toms 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](#_bookmark5)], 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](#_bookmark26)]. Further, both missense and frameshifting variants in trans with the p.Leu304Arg variant have been associated with AHS [[40](#_bookmark28), [41](#_bookmark31)]. Other missense variants in combination with the p.Leu304Arg allele have been associated with SANDO and AR PEO, respectively [[38](#_bookmark24), [42](#_bookmark32)]. 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](#_bookmark36), [43](#_bookmark35)].

Conclusion

This is a case of a young boy, who carried homozygous *POLG* mutations and demonstrated a series of symp- toms 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.

Acknowledgements The authors thank the patient and family for the participation in the study. Parental consent was obtained for publishing the case report.

Funding This work was supported by the Foundation Fighting Blindness, USA (Grant No: CD-CL-0617-0727-HSC). The funding organization had no role in the design or conduct of this research. AV is a consultant for ADVERUM Biotechnologies INC; this had no role in the design or conduct of the research.

Compliance with ethical standards

Statement of human rights The study was approved by the Research Ethics Board at the Hospital for Sick Children Tor- onto. The study protocols adhered to the tenets of the Declara- tion 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.

References

1. Kong YX, Van Bergen N, Trounce IA, Bui BV, Chrysos- tomou V, Waugh H et al (2011) Increase in mitochondrial DNA mutations impairs retinal function and renders the retina vulnerable to injury. Aging Cell 10(4):572–583
2. DeBalsi KL, Hoff KE, Copeland WC (2017) Role of the mitochondrial DNA replication machinery in mitochondrial DNA mutagenesis, aging and age-related diseases. Ageing Res Rev 33:89–104
3. Zheng W, Khrapko K, Coller HA, Thilly WG, Copeland WC (2006) Origins of human mitochondrial point mutations as DNA polymerase gamma-mediated errors. Mutat Res 599(1–2):11–20
4. Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE et al (2005) Mitochondrial DNA muta- tions, oxidative stress, and apoptosis in mammalian aging. Science 309(5733):481–484
5. Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE et al (2004) Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature 429(6990):417–423
6. Farnum GA, Nurminen A, Kaguni LS (2014) Mapping 136 pathogenic mutations into functional modules in human DNA polymerase gamma establishes predictive genotype- phenotype correlations for the complete spectrum of POLG syndromes. Biochim Biophys Acta 1837(7):1113–1121
7. Cohen BH, Chinnery PF, Copeland WC (1993) POLG-re- lated disorders. In: Adam MP, Ardinger HH, Pagon RA,

Wallace SE, Bean LJH, Stephens K, et al. (eds) GeneRe- views((R)). University of Washington, Seattle

1. Filosto M, Mancuso M, Nishigaki Y, Pancrudo J, Harati Y, Gooch C et al (2003) Clinical and genetic heterogeneity in progressive external ophthalmoplegia due to mutations in polymerase gamma. Arch Neurol 60(9):1279–1284
2. Luoma P, Melberg A, Rinne JO, Kaukonen JA, Nupponen NN, Chalmers RM et al (2004) Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. Lancet 364(9437):875–882
3. Van Goethem G, Luoma P, Rantamaki M, Al Memar A, Kaakkola S, Hackman P et al (2004) POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement. Neurology 63(7):1251–1257
4. Van Goethem G, Dermaut B, Lofgren A, Martin JJ, Van Broeckhoven C (2001) Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. Nat Genet 28(3):211–212
5. Van Goethem G, Martin JJ, Dermaut B, Lofgren A, Wibail A, Ververken D et al (2003) Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthal- moplegia. Neuromuscul Disord 13(2):133–142
6. Lamantea E, Tiranti V, Bordoni A, Toscano A, Bono F, Servidei S et al (2002) Mutations of mitochondrial DNA polymerase gammaA are a frequent cause of autosomal dominant or recessive progressive external ophthalmople- gia. Ann Neurol 52(2):211–219
7. Saneto RP, Cohen BH, Copeland WC, Naviaux RK (2013) Alpers–Huttenlocher syndrome. Pediatr Neurol 48(3):167–178
8. Harding BN (1990) Progressive neuronal degeneration of childhood with liver disease (Alpers–Huttenlocher syn- drome): a personal review. J Child Neurol 5(4):273–287
9. Worle H, Kohler B, Schlote W, Winkler P, Bastanier CK (1998) Progressive cerebral degeneration of childhood with liver disease (Alpers Huttenlocher disease) with cyto- chrome oxidase deficiency presenting with epilepsia par- tialis continua as the first clinical manifestation. Clin Neuropathol 17(2):63–68
10. Hakonen AH, Heiskanen S, Juvonen V, Lappalainen I, Luoma PT, Rantamaki M et al (2005) Mitochondrial DNA polymerase W748S mutation: a common cause of autoso- mal recessive ataxia with ancient European origin. Am J Hum Genet 77(3):430–441
11. Di Fonzo A, Bordoni A, Crimi M, Sara G, Del Bo R, Bre- solin N et al (2003) POLG mutations in sporadic mito- chondrial disorders with multiple mtDNA deletions. Hum Mutat 22(6):498–499
12. Audo I, Robson AG, Holder GE, Moore AT (2008) The negative ERG: clinical phenotypes and disease mechanisms of inner retinal dysfunction. Surv Ophthalmol 53(1):16–40
13. Nguyen KV, Sharief FS, Chan SS, Copeland WC, Naviaux RK (2006) Molecular diagnosis of Alpers syndrome. J Hepatol 45(1):108–116
14. Boyd SG, Harden A, Egger J, Pampiglione G (1986) Pro- gressive neuronal degeneration of childhood with liver disease (‘‘Alpers’ disease’’): characteristic neurophysio- logical features. Neuropediatrics 17(2):75–80
15. Marmor MF, Holder GE, Seeliger MW, Yamamoto S, International Society for Clinical Electrophysiology of V

(2004) Standard for clinical electroretinography (2004 update). Doc Ophthalmol 108(2):107–114

1. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R et al (2015) ISCEV standard for full- field clinical electroretinography (2015 update). Doc Oph- thalmol 130(1):1–12
2. Hanisch F, Kornhuber M, Alston CL, Taylor RW, Deschauer M, Zierz S (2015) SANDO syndrome in a cohort of 107 patients with CPEO and mitochondrial DNA dele- tions. J Neurol Neurosurg Psychiatry 86(6):630–634
3. Wong LJ, Naviaux RK, Brunetti-Pierri N, Zhang Q, Schmitt ES, Truong C et al (2008) Molecular and clinical genetics of mitochondrial diseases due to POLG mutations. Hum Mutat 29(9):E150–E172
4. Finsterer J, Zarrouk MS (2012) Epilepsy in mitochondrial disorders. Seizure 21(5):316–321
5. Fadic R, Russell JA, Vedanarayanan VV, Lehar M, Kuncl RW, Johns DR (1997) Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neu- rology 49(1):239–245
6. Young MJ, Longley MJ, Li FY, Kasiviswanathan R, Wong LJ, Copeland WC (2011) Biochemical analysis of human POLG2 variants associated with mitochondrial disease. Hum Mol Genet 20(15):3052–3066
7. Milone M, Massie R (2010) Polymerase gamma 1 muta- tions: clinical correlations. Neurologist 16(2):84–91
8. Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S et al (2006) The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. Brain 129(Pt 7):1685–1692
9. Stumpf JD, Saneto RP, Copeland WC (2013) Clinical and molecular features of POLG-related mitochondrial disease. Cold Spring Harb Perspect Biol 5(4):a011395
10. Pagnamenta AT, Taanman JW, Wilson CJ, Anderson NE, Marotta R, Duncan AJ et al (2006) Dominant inheritance of premature ovarian failure associated with mutant mito- chondrial DNA polymerase gamma. Hum Reprod 21(10):2467–2473
11. Pillers DA, Fitzgerald KM, Duncan NM, Rash SM, White RA, Dwinnell SJ et al (1999) Duchenne/Becker muscular dystrophy: correlation of phenotype by electroretinography with sites of dystrophin mutations. Hum Genet 105(1–2):2–9
12. Rahman S, Copeland WC (2019) POLG-related disorders and their neurological manifestations. Nat Rev Neurol 15(1):40–52
13. Naimi M, Bannwarth S, Procaccio V, Pouget J, Desnuelle C, Pellissier JF et al (2006) Molecular analysis of ANT1, TWINKLE and POLG in patients with multiple deletions or depletion of mitochondrial DNA by a dHPLC-based assay. Eur J Hum Genet 14(8):917–922
14. Tang S, Wang J, Lee NC, Milone M, Halberg MC, Schmitt ES et al (2011) Mitochondrial DNA polymerase gamma mutations: an ever expanding molecular and clinical spec- trum. J Med Genet 48(10):669–681
15. Sonam K, Bindu PS, Srinivas Bharath MM, Govindaraj P, Gayathri N, Arvinda HR et al (2017) Mitochondrial oxidative phosphorylation disorders in children: pheno- typic, genotypic and biochemical correlations in 85 patients from South India. Mitochondrion 32:42–49
16. Rouzier C, Chaussenot A, Serre V, Fragaki K, Bannwarth S, Ait-El-Mkadem S et al (2014) Quantitative multiplex PCR of short fluorescent fragments for the detection of large intragenic POLG rearrangements in a large French cohort. Eur J Hum Genet 22(4):542–550
17. Stewart JD, Horvath R, Baruffini E, Ferrero I, Bulst S, Watkins PB et al (2010) Polymerase gamma gene POLG determines the risk of sodium valproate-induced liver tox- icity. Hepatology 52(5):1791–1796
18. Navarro-Sastre A, Tort F, Garcia-Villoria J, Pons MR, Nascimento A, Colomer J et al (2012) Mitochondrial DNA depletion syndrome: new descriptions and the use of citrate synthase as a helpful tool to better characterise the patients. Mol Genet Metab 107(3):409–415
19. Cardenas JF, Amato RS (2010) Compound heterozygous polymerase gamma gene mutation in a patient with Alpers disease. Semin Pediatr Neurol 17(1):62–64
20. Scuderi C, Borgione E, Castello F, Lo Giudice M, Santa Paola S, Giambirtone M et al (2015) The in cis T251I and P587L POLG1 base changes: description of a new family and literature review. Neuromuscul Disord 25(4):333–339
21. Horvath R, Hudson G, Ferrari G, Futterer N, Ahola S, Lamantea E et al (2006) Phenotypic spectrum associated with mutations of the mitochondrial polymerase gamma gene. Brain 129(Pt 7):1674–1684

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.