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Ocular evaluation and genetic test for an early Alström Syndrome diagnosis

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A R T I C L E I N F O

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A B S T R A C T

Purpose: We present 3 cases of Alström syndrome (ALMS) that highlight the importance of the ophthalmic exam, as well as the diagnostic challenges and management considerations of this ultra-rare disease.
Observations: The first case is of a 2-year-old boy with history of spasmus nutans who presented with head bobbing and nystagmus. The second patient is a 5-year-old boy with history of infantile dilated cardiomyopathy status post heart transplant, Burkitt lymphoma status post chemotherapy, obesity, global developmental delay, and high hyperopia previously thought to have cortical visual impairment secondary to heart surgery/possible ischemic event. This patient presented with nystagmus, photophobia, and reduced vision. The third case involves a 8-year-old boy with history of obesity, bilateral optic nerve atrophy, hyperopic astigmatism, exotropia, and nystagmus. Upon presentation to the consulting pediatric ophthalmologist, none of the patients had yet been diagnosed with ALMS. All 3 cases were subsequently found to have an electroretinogram (ERG) that exhibited severe global depression and to carry *ALMS1* pathogenic variants.
Conclusions and Importance: ALMS is an autosomal recessive disease caused by *ALMS1* variations, characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing loss, cardiomyopathy, insulin resistance, and multiorgan dysfunction. Retinal dystrophy diagnosis is critical given clinical criteria and detection rates of genetic testing. Early diagnosis is extremely important because progression to flat ERG leads to the inability to differentiate between rod-cone or cone-rod involvement, either of which have their own differential diagnoses. In our series, the ophthalmic exam and abnormal ERG prompted further genetic testing and the subsequent diagnosis of ALMS. Multidisciplinary care ensures the best possible outcome with the ophthalmologist playing a key role.

1. Introduction

According to Alström Syndrome International, approximately 1053 cases of Alström Syndrome (ALMS; OMIM #203800) have been reported worldwide.[1] The estimated prevalence ranges from 1 in 10,000 to 1 in 1, 000,000.[2,3] The disease is caused by mutations in the *ALMS1* gene. The ALMS1 protein is found at low levels in most tissues, which explains the multiorgan involvement.[4] Although the extent of the ALMS1 protein's biologic function is under investigation, it is essential for ciliary structure and function, ciliary signaling pathways, intracellular trafficking, cell differentiation, and metabolic homeostasis.[5] Therefore, ALMS is categorized as a ciliopathy and should be included with other ciliopathies such as Bardet-Biedl and Joubert syndrome when forming a differential diagnosis. ALMS follows an autosomal recessive inheritance pattern characterized by complete penetrance, but significant variable expressivity. There have been 268 disease-causing mutations identified in the *ALMS1* gene.[6,7] The majority are single-nucleotide substitutions leading to codon termination (nonsense) and frameshift changes (deletions, duplications, and insertions). Most variants are reported in exons 8 (51.5%), 16 (17.3%), and 10 (16%), that can be considered as hotspots of *ALMS1*.

Patients with ALMS usually have normal birth weight. However,

Abbreviations: ALMS, Alström Syndrome; APD, Afferent pupillary defect; BMI, Body mass index; CHF, Congestive heart failure; CLIA, Clinical Laboratory Improvement Amendments; DA, Dark-adapted; DFE, Dilated fundus exam; EEG, Electroencephalogram; ERG, Electroretinogram; EUA, Exam under anesthesia; FAF, Fundus autofluorescence; IGF, Insulin-like growth factor; IR, Insulin resistance; ISCEV, International Society for Clinical Electrophysiology of Vision; OCT, Optical coherence tomography; OD, Right eye; OPs, Oscillatory potentials; OS, Left eye; OU, Both eyes; LA, Light-adapted; MRI, Magnetic resonance imaging; RPE, Retinal pigment epithelium; T2DM, Type II diabetes mellitus; VA, Visual acuity; VEP, Visual evoked potential; VGB, Vigabatrin; cDNA, complementary DNA.

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hyperphagia and excessive weight gain due to insulin resistance (IR), especially truncal, results in early childhood obesity with a body mass index (BMI) ≥25 or a BMI ≥95th percentile for age. IR leading to type 2 diabetes mellitus (T2DM) usually develops in childhood. The metabolic abnormalities are typically accompanied by skin changes, such as acanthosis nigricans, as well as dyslipidemia and early-onset coronary artery disease. Approximately 40% of patients develop dilated cardiomyopathy, typically in infancy,[8] and 20% develop restrictive cardiomyopathy, usually during early adolescence into adulthood. Over 60% of patients develop congestive heart failure (CHF) secondary to cardiomyopathy.[9] Dilated cardiomyopathy or CHF are frequent causes of death.[5] Progressive bilateral sensorineural hearing loss, initially involving the high-frequency range, presents in infancy in 88% of patients.[10] Approximately 20% experience delay in reaching early developmental milestones, specifically gross and fine motor skills, as well as expressive and receptive language, perhaps due to vision and hearing impairment. Despite the developmental delay, cognitive impairment is very rare. Lung involvement ranges from bronchial infections to pulmonary fibrosis and hypertension. Liver involvement typically occurs after childhood and includes fibrosis, cirrhosis, portal hypertension, and liver failure. Glomerulosclerosis progressing to end-stage renal disease presents from adolescence through adulthood. The incidence is variable, but highest during the third decade of life.

Cone-rod dystrophy affects all individuals with ALMS and typically presents between birth and 15-months of age. However, like other features of ALMS, the age of onset and severity of disease varies. Interestingly, pathologic variants in exon 16 of *ALMS1* have been associated with the onset of retinal dystrophy before one year of age.[11] The retinal dystrophy is progressive, leading to visual impairment, severe photophobia on the level of photodysphoria, and nystagmus.[12] We report the visual symptoms, ophthalmic exam findings, and electroretinogram (ERG) results (RET*eval*, LKC Technologies, Inc.) using International Society for Clinical Electrophysiology of Vision (ISCEV) standard protocol of three cases of ALMS. The ophthalmic exam and ERG findings led to the diagnosis of ALMS. All three cases were referred to and examined at the University of Wisconsin-Madison Department of Ophthalmology and Visual Sciences' Inherited Retinal Degeneration Clinic. These cases highlight the diagnostic challenges and management considerations of this ultra-rare disease.

1.1. Case series

1.2. Case 1

The first patient was a 2-year-old boy born full-term at the 99th percentile for weight. He was diagnosed with spasmus nutans by a pediatric neurologist due to abnormal head movement and nystagmus. The mother first noted horizontal and vertical head bobbing with nystagmus in the weeks prior to examination by the referring pediatric ophthalmologist. The patient met all developmental milestones. Previous electroencephalogram (EEG) was without lateralized features or epileptiform discharges and was within normal limits for age.

On the initial examination by the referring pediatric ophthalmologist, visual acuity (VA) was central, steady, and maintained. Pupils were equal round and reactive to light without afferent pupillary defect (APD). Bruckner test was equal bilaterally. Strabismus exam via Krimsky method demonstrated that the patient was ortho at near. Very fine horizontal and vertical conjugate nystagmus with rapid horizontal head bobbing was observed. Slit lamp and dilated fundus exam (DFE) were normal. Retinoscopy showed high hyperopia (+7.50 OD and +8.00 OS). A prior head magnetic resonance imaging (MRI) demonstrated a 2 mm non-enhancing cystic lesions between the anterior and posterior lobes of the pituitary gland likely representing a pars media/Rathke's cleft cyst but was otherwise without suspicious structural brain abnormalities. He was diagnosed with spasmus nutans and carried this diagnosis for some time prior to presentation.

At the six-month follow-up with the referring pediatric ophthalmologist, the patient was squinting more often. Examination showed no head bobbing but was otherwise unchanged. Cycloplegic refraction via retinoscopy confirmed high hyperopia (+7.50 OD and +8.50 + 0.75 × 075 OS) and corrective lenses were prescribed. At the nine-month follow-up visit, visual evoked potential (VEP) demonstrated reduced amplitude and delay of the prominent positive wave. DFE was unable to be obtained due to poor cooperation.

At twelve-month follow up, squinting persisted, and the patient was now sensitive to light. Additionally, he had been running into things for the past few months. On examination, the patient was very photophobic, and DFE was unable to be obtained. An exam under anesthesia (EUA) was performed along with a full-field electroretinogram (ERG) using a Diagnosys E2 system (Diagnosys, LLC, Lowell, Mass). The ISCEV standard protocol 20 min dark-adaptation (DA) and 10 min light-adaptation (LA) at 30 cd m^{-2} was followed. The optional DA red flash condition was included. The EUA demonstrated increased macular pigmentation and retinal pigment epithelium mottling in the periphery and mid-periphery. The ERG demonstrated severely diminished cone and rod responses. The cone-mediated single flash LA 3.0 and the LA 30 Hz flicker and DA red responses were not recordable. A reduced amplitude ERG to the DA 3.0 is consistent with some residual rod function (Fig. 1). For comparison, Fig. 1 presents an ERG recorded from a 2.3-year-old boy while under anesthesia for screening for vigabatrin, demonstrating well-developed cone-mediated ERG at this age. This patient is age-matched for our Case 1 and a control for possible effect of anesthesia on the ERG.

Follow-up exam in the Inherited Retinal Degeneration Clinic showed VA was central, unsteady, and maintained. The pupillary exam was normal. Strabismus exam via alternate cover test demonstrated ortho at distance and near. The patient was unable to hold fixation very long. Intermittent nystagmus and narrow interpalpebral fissures were observed. The portable slit lamp exam was normal. Based on the ophthalmic exam and ERG results, a comprehensive retinal dystrophy panel at a Clinical Laboratory Improvement Amendments (CLIA)-certified lab was recommended which identified two pathogenic mutations in *ALMS1*: a new nonsense substitution c.10936C > T, p.(Gln3646*) in exon 16 and a deletion c.11703del, p.(Lys3901ASnfs*8) in exon 18 previously described (Table 2).[6,7] The parental testing confirmed these variants were inherited in *trans* and the Case 1 is a compound heterozygote.

Upon diagnosis, the patient was connected with medical genetics and referrals were placed for baseline evaluation in audiology, urology, nutrition/gastroenterology, endocrinology, and cardiology. Further workup revealed elevated triglycerides and the family has been working on dietary intervention. Possible mild hearing loss with middle ear involvement and undescended testes were also discovered.

1.3. Case 2

A 5-year-old full-term boy born at the 7th percentile for weight with a history of infantile dilated cardiomyopathy status post heart transplant, Burkitt lymphoma status post chemotherapy, obesity, global developmental delay, and high hyperopia was referred by an optometrist to pediatric ophthalmology. The patient squinted while outside in sunlight and the father noted horizontal nystagmus for the last four years that improved slightly after receiving corrective lenses. The nystagmus began shortly after the patient's heart surgery and was thought to be due to cortical visual impairment as a result of possible ischemic event during heart surgery. The patient was tested by an outside physician for Hermansky-Pudlak syndrome, a syndromic form of albinism, and testing was negative. The patient had difficulty negotiating varying ground levels and seeing at distance. He has worn corrective lenses for approximately three years. The father has a history of early onset cataract at age four. Family history was otherwise negative.

On examination by the referring pediatric ophthalmologist, VA

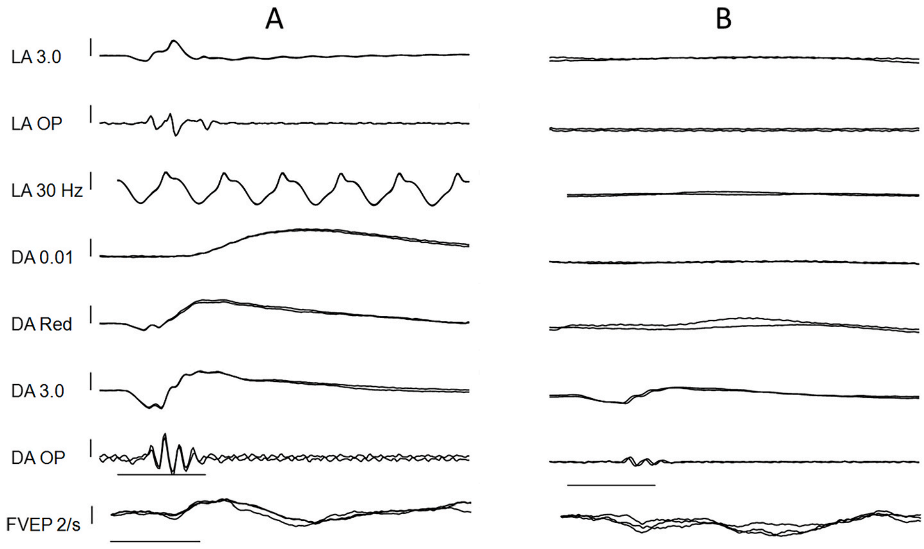

Fig. 1. Light-adapted (LA) and dark-adapted (DA) electroretinogram ERGs recorded under anesthesia from a 2.3-year-old boy taking vigabatrin (VGB) who has shown no evidence of toxicity (**A**), and Case 1 tested at 2.25 years of age (**B**). Right and left eye ERGs are superimposed. The cone-mediated ERGs (LA 3.0, LA OPs, LA 30 Hz, and DA Red) are non-recordable in Case 1 (**B**) whereas corresponding cone ERGs are robust in the VGB patient (**A**). In addition, the DA 0.01 rod-mediated ERG, mixed DA 3.0, and the DA OPs are robust in the VGB patient but are markedly diminished in Case 1. The bright DA 3.0 cd-s m^{-2} flash elicited comparatively small amplitude A- and B-waves and markedly diminished DA OPs. ERG amplitude calibration: 100 μV, except OPs, which are 20 μV. ERG time calibration: 50 ms marked from onset of flash. Bottom two panels show binocular flash visual evoked potential (VEP) recorded unsedated within a month of the ERG recordings for each patient. Compared with the VGB patient, the negative/positive flash VEP complex is delayed and diminished in amplitude for Case 1. VEP vertical calibration: 8 μV; horizontal calibration: 100 ms from flash onset (single flash ERGs begin recording 20 ms pre-flash).

Table 1
Clinical and Ophthalmological comparison of cases.

	Case 1	Case 2	Case 3
Age of clinic visit	2 years	5 years	8 years
Gender	Male	Male	Male
Presenting signs	Head bobbing and nystagmus	Photophobia, nystagmus, and decreased vision	Nystagmus, strabismus, and photophobia
Past medical history	Spasmus nutans	Infantile dilated cardiomyopathy status post heart transplant, Burkitt lymphoma status post chemotherapy, obesity, global developmental delay, and high hyperopia	Bilateral optic nerve atrophy, hyperopic astigmatism, exotropia, and nystagmus
Family history	None	Father with early onset cataract at 4 years old	Albinism (nystagmus and red hair) in children of first-cousin marriage
Visual acuity	Central, steady, and maintained OU	20/200 OD 20/100 OS	20/400 OD at 13′ 20/400 OS at 10′
Electroretinography Summary	Severely diminished rod and cone response	Severely diminished rod and cone response	Severely diminished rod and cone response

measured 20/200 OD and 20/100 OS. Pupils were equal at 4 mm in the dark, round, and minimally reactive to light without APD. Very fine rapid horizontal conjugate asymmetric nystagmus with right eye greater than left eye. There was also an intermittent vertical component. Poor fixation was seen in both eyes (left greater than right). The slit lamp exam was unremarkable. DFE showed less defined disc margin in the right eye but was otherwise normal. Cycloplegic refraction confirmed high hyperopia ($+8.50 + 1.00 \times 090$ OD and $+8.00 + 1.00 \times 090$ OS). Full-field RET*eval* (LKC Technologies, Inc.) ERG in this patient was flat to the DA 10.0 condition (not shown).

Four months later the patient was first examined at the Inherited Retinal Degeneration Clinic. The VA with correction was 20/400 bilaterally at distance and 20/80 at 3 inches. The patient was unable to distinguish color on Ishihara or Hardy Rand and Ritler pseudoisochromatic plates. A small exotropia was noted on strabismus exam. A fine shimmering rotary nystagmus was also seen. DFE demonstrated waxy pallor of the optic disc, blunted foveal reflex, and mild vascular attenuation bilaterally. The right optic disc margin was less defined but without edema or elevation. A large retinal dystrophy panel at CLIA-certified lab was ordered and identified 2 new pathogenic variants in *ALMS1*: a deletion in exon 5 c.1199_1205del, p.(Thr400Lysfs*11) and a deletion encompassing exon 1 c.(?_-1)_(327 + 1_328–1)del. The latter variant, even if not deeply characterized at transcript level, is of extreme interest because so far, no pathogenic variants have been described in exon 1 of *ALMS1* (Table 2).[6,7] The parental testing confirmed these variants were inherited in *trans* and the Case 2 is a compound heterozygote.

Table 2
Genotype comparison of cases.

	Case 1		Case 2		Case 3	
cDNA Variant	c.10936C > T	c.11703del	c.1199_1205del	c.(?_-1)_(327 + 1_328–1)del	c.11416C > T	c.11086dup
Variant Type	Nonsense	Frameshift	Frameshift	Partial gene deletion	Nonsense	Frameshift
Exon Affected	16	18	5	1	16	16
Predicted Protein	p.(Gln3646*)	p.(Lys3901ASnfs*8)	p.(Thr400Lysfs*11)	N/A	p.(Arg3806*)	p.(Ser3696Lysfs*13)
Previously Described	No, new variant	Yes, Marshall JD et al., 2015 and Astuti et al., 2017	No, new variant	No, new variant	Yes, Bond et al., 2005 and Minton et al., 2006	No, new variant

1.4. Case 3

An 8-year-old boy with history of bilateral optic nerve atrophy, hyperopic astigmatism, exotropia, and nystagmus was referred from an outside pediatric ophthalmologist for evaluation of possible retinal dystrophy. The mother noted nystagmus and misalignment at nine months, and photophobia at around two years of age. The patient had difficulty identifying colors. Family history was significant for albinism (nystagmus and red hair) in the children of a first-cousin marriage. Prior brain MRI with and without contrast to evaluate for the etiology of optic nerve atrophy was without intracranial findings. The optic nerve atrophy was thought to be related to prior meningitis at age 4 months. However, on further questioning the family denied any lumbar puncture or other evaluation for the patient's fever at that time of the presumed meningitis.

On examination, the VA was 20/400 at 13 feet OD, 20/400 at 10 feet OS, 20/400 at 16 feet OU, and 20/160 at 7 cm OU. The pupillary exam was normal. The strabismus exam via Krimsky method demonstrated 35 prism diopters of exotropia at near. A horizontal/pendular high frequency small amplitude nystagmus was noted. The slit lamp exam was normal. DFE was deferred by the family secondary to photophobia. Cycloplegic refraction (+2.50 + 2.75 × 090 OD and +2.75 + 3.50 × 090 OS). Full-field RET*eval* (LKC Technologies, Inc.) ERG revealed severely diminished rod and cone responses in both eyes. As with Case 2, no ERG could be recorded, including to the DA 10 flash strength (not shown). A large retinal dystrophy panel at CLIA-certified lab identified 2 heterozygous variants of *ALMS1*: a nonsense substitution in exon 16 c.11416C > T, p.(Arg3806*) previously described[2,13] and a new duplication in exon 16 *ALMS1* c.11086dup, p.(Ser3696Lysfs*13) (Table 2). The parental testing confirmed these variants were inherited in *trans* and the Case 3 is a compound heterozygote.

The patient was seen in follow-up by audiology, endocrinology, gastroenterology, and cardiology. He was found to have unilateral high frequency hearing loss. Endocrinology identified elevated triglycerides, elevated insulin, and signs of IR. Hepatic steatosis was found on ultrasound. Low insulin-like growth factor (IGF)-binding protein 1 and normal IGF-binding protein 3 were discovered. The patient is therefore being monitored for possible growth hormone deficiency.

On follow-up exam, the VA was observed to be 2'/200 OD and 8'/200 OS. The pupillary exam was normal and large exotropia was unchanged from the previous examination. The slit lamp exam showed mild blepharitis but was otherwise within normal limits. DFE demonstrated mild diffuse pallor of the optic disc, blunted foveal reflex, severe vascular attenuation, and diffuse hypopigmented mottling bilaterally (Fig. 2A). Fundus autofluorescence (FAF) (Fig. 2B) and optical coherence tomography (OCT) (Fig. 2C) were obtained. FAF showed a circular region of decreased autofluorescence encompassing the macula surrounded by a ring of increased autofluorescence in both eyes. OCT was limited due to cooperation but demonstrated distorted foveal contour with loss of the outer retina, specifically the photoreceptor layer, within the macula of both eyes. Cycloplegic refraction (+2.00 + 3.75 × 085 OD and +2.50 + 4.00 × 090 OS). The patient was referred for low vision services.

2. Discussion

Pathogenic variants of *ALMS1* are increasingly being identified by molecular genetic testing in individuals with ALMS.[14] However, significant variation in detection rates may highlight the limitations of genetic testing in diagnosing ALMS. Interestingly, no other phenotypes caused by pathogenic variants in *ALMS1* have been identified, which may have implications for understanding of the molecular mechanisms and provide a basis for further investigation of how variants in *ALMS1* contribute to the severity of disease.[4] The diagnosis of ALMS is supported by the identification of at least one pathogenic variant of *ALMS1*. However, it is important to note that failure to identify a disease-causing variant in *ALMS1* does not rule out a diagnosis of ALMS. Although numerous pathogenic and likely pathogenic variants have been discovered, novel variants are not infrequently identified.[6, 7]In this case series we identified four new pathogenic *ALMS1* variants in patients with ALMS.

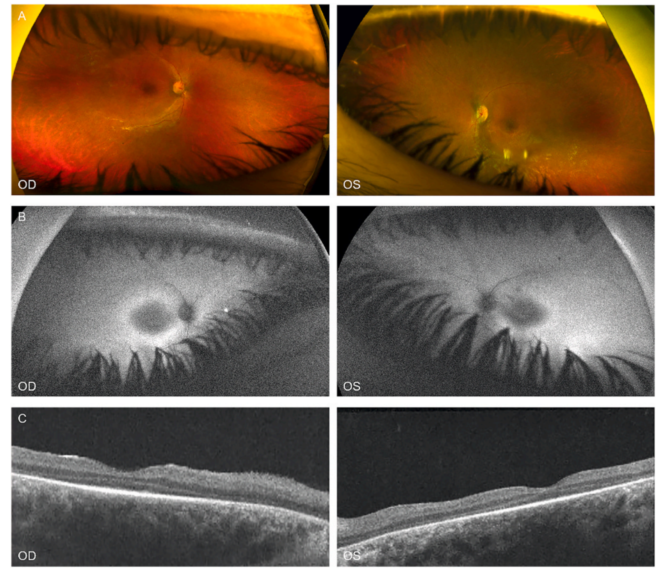

Fig. 2. Bilateral fundus photograph, fundus autofluorescence (FAF), and optical coherence tomography (OCT) images for Case 3. (**A**) Fundus photographs showing mild diffuse pallor of the optic disc, blunted foveal reflex, severe vascular attenuation, and diffuse hypopigmented mottling bilaterally. (**B**) FAF demonstrating a circular region of decreased autofluorescence encompassing the macula surrounded by a ring of increased autofluorescence bilaterally. (**C**) OCT with distorted foveal contour with loss of the outer retina, specifically the photoreceptor layer, within the macula bilaterally.

Although there is a wide range of clinical variability,[9] the diagnosis of ALMS is based on clinical features that present throughout infancy, childhood, and young adulthood. Marshall et al. created diagnostic criteria stratified by age using major and minor features.[15] Major features include cone-rod dystrophy, sensorineural hearing loss, obesity, IR/T2DM, cardiomyopathy, pulmonary, liver, and renal disease. Genetic testing, cardiomyopathy, and cone-rod dystrophy are the only major diagnostic features of ALMS at less than 2 years of age. Cone-rod dystrophy is universal at less than 2 years of age, while cardiomyopathy is not; however, the diagnosis of cardiomyopathy can assist with the management of the deadliest feature of ALMS early on. Retinal dystrophy, the only universal finding in ALMS, is nonspecific and may lead to delay in diagnosis or misdiagnosis, particularly without the input of an ophthalmologist. Minor features include hypothyroidism, hypogonadism in men and hyperandrogenism in women. Delay in reaching developmental milestones, urologic dysfunction/detrusor instability, distinct facial features (e.g. round face, premature frontal balding, thin hair, and deep-set eyes), dental abnormalities (e.g., discolored enamel bands), wide flat feet, tonic-clonic seizures, and abnormal head imaging findings, such as empty sell turcica and hyperostosis frontalis interna are minor features in all genders.

All three of our patients presented with nystagmus (Table 1). Case 2 and 3 presented with photophobia, and Case 1 later developed photophobia. In general, patients with ALMS display a VA of 6/60 or less by ten years of age and no light perception by 20 years of age.[16] VA at presentation in Case 2 was 20/200 OD and 20/100 OS. Case 3 VA was 20/400 at 13 feet OD and 20/100 at 10 feet OS. Hyperopia, ranging from mild to high, has been reported in ALMS.[12,17] All three of our patients also presented with hyperopia, including two with high hyperopia (Case 1 and 2) and one with moderate hyperopia (Case 3). Examination of the fundus within the first year of life may be normal or may demonstrate pale optic discs with narrowing of the retinal vessels. Crystalline retinal deposits have been observed.[12] EUA of Case 1 demonstrated increased macular pigmentation and RPE mottling in the periphery and mid-periphery. The fundus exam of Case 2 when examined showed waxy pallor of the optic disc, blunted foveal reflex, and mild vascular attenuation bilaterally. The fundus exam of Case 3 showed mild diffuse pallor of the optic disc, blunted foveal reflex, severe vascular attenuation, and diffuse hypopigmented mottling bilaterally. Posterior subcapsular cataracts are common, even without associated T2DM. Optical coherence tomography (OCT) findings are often absent to mild during the first decade of life and progress to disruption of the normal retinal architecture, severe retinal wrinkling, hyperreflective foci throughout all retinal layers, loss of photoreceptors and the RPE, increased choroidal vasculature, optic nerve drusen, and vitreoretinal separation.[18] The OCT of Case 3 showed distortion of the foveal contour and loss of the photoreceptor layer bilaterally.

Due to the early-onset retinal dystrophy, ophthalmologists have a unique opportunity to aid in the diagnosis of ALMS, with ERG playing a vital role. All three of our patients presented with nystagmus and the ERG demonstrated a severely diminished cone and rod response. The ophthalmic work-up is what ultimately led to the diagnosis of ALMS in all three of our patients. ERG is essential for diagnosis and is typically abnormal from birth with progressive involvement of both cones and rods.[17] Obtaining an ERG early provides the opportunity to differentiate between rod-cone or cone-rod involvement, either of which have their own differential diagnosis. The most common initial test for children with nystagmus is brain MRI; however, the most common cause of infantile nystagmus is a retinal disorder.[19] Ideally, children presenting with isolated nystagmus should undergo complete ophthalmic examination, ERG, OCT, and molecular genetic testing.[12] Unfortunately, the use of ERG may be limited by the risks and costs of sedation for young children requiring EUA, limited access, and lack of insurance coverage. However, non-sedated handheld cone flicker ERG may serve as a feasible screening test to detect retinal dysfunction in children presenting with nystagmus.[20] In a large study assessing the clinical use and efficacy of electrophysiology testing in children referred to a visual electrophysiology laboratory in Singapore, ERG was abnormal in 70% of patients with the most common diagnosis being retinal dystrophy/-dysfunction or optic nerve/cortical dysfunction.[21] The most common reason for referral was poor vision, and 13% of patients were referred for evaluation of nystagmus. Earlier ERG in our patients would have resulted in sooner diagnosis and referral for management of multiorgan dysfunction.

The differential diagnosis of ALMS includes syndromic disorders, such as Bardet-Biedl syndrome (BBS) and inherited mitochondrial disorders, and non-syndromic disorders, such as Leber congenital amaurosis (LCA) and achromatopsia[16] The major features of BBS include rod-cone dystrophy, cognitive impairment, central obesity, polydactyly, hypogonadism, and renal dysfunction.[22] Although many features overlap with ALMS, the timing of retinal degeneration captured by ERG can help distinguish the two. Retinal degeneration in ALMS initially involves the cones and progresses to both cone and rod involvement, whereas BBS usually begins with rod involvement and progresses to both rod and cone. BBS presents with visual symptoms around eight years of age, whereas ALMS presents within the first two years of life. Additionally, ALMS typically does not present with polydactyly. Overlapping features of inherited mitochondrial disorders and ALMS include pigmentary retinopathy, optic atrophy, sensorineural hearing loss, cardiomyopathy, and T2DM. Muscle and central nervous system involvement of inherited mitochondrial disorders have not been reported in ALMS.

Once a diagnosis of ALMS is made, a multidisciplinary team should be established. The patient's weight, height, and BMI should be recorded yearly, along with audiometry testing. A cardiac evaluation, including echocardiography and ECG, should be performed yearly. Fasting plasma glucose should be tested every two to three months. Plasma insulin and lipid profile should be obtained yearly. Urinalysis and plasma electrolytes, uric acid, BUN, and creatinine should be obtained biannually. Liver enzymes should be obtained yearly, and abdominal ultrasound for liver evaluation should be performed. Pulmonary function testing and thyroid function testing should be conducted yearly. Consultation with a clinical geneticist and/or genetic counselor should be made, with or without carrier testing for at-risk family members.

Unfortunately, there is no therapy to prevent progressive multiorgan dysfunction. However, clinical trials targeting the inflammatory and fibrotic features are underway.[23,24] To address the cone-rod dystrophy, red-orange tinted prescription lenses may reduce photophobia. Low vision specialists can assess the need for aids such as large print reading materials, Braille, mobility training, and adaptive living skills. Smartphone, tablets, and voice activated technologies are useful in everyday life.[25]

3. Conclusions

ALMS is an ultra-rare autosomal recessive disease caused by mutations in the *ALMS1* gene, characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing loss, cardiomyopathy, IR, and multiorgan dysfunction. The diagnosis is based on clinical findings, family history, and molecular genetic testing. Although there is no cure, ophthalmologists can make the diagnosis early, allowing multidisciplinary care to ensure the best possible outcome.

Patient consent

The patient's legal guardians provided consent to publication of the cases orally.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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