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Neovascularization of the optic disc and peripheral retinal ischemia in a child with a novel variant in *ALMS1* (Alström syndrome)

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ABSTRACT

Purpose: The ophthalmologic findings in Alström syndrome include cone-rod dystrophy, optic atrophy, optic disc drusen, and retinal telangiectasias with exudative retinopathy. Here we describe peripheral retinal non-perfusion with neovascularization of the disc (NVD) in a child with Alström syndrome-related cone-rod dystrophy.

Observations: A six-year-old girl with a diagnosis of Alström syndrome based on a homozygous nonsense likely pathogenic variant in *ALMS1* (NM_015120.4:c.4746C > G; p.Tyr1582Ter) was seen in the ophthalmology clinic for nystagmus, photophobia, and poor vision with non-recordable scotopic and photopic electroretinography (ERG) responses. On routine follow-up exam, she was found to have optic disc hyperemia and apparent swelling. Brain and orbital magnetic resonance imaging (MRI) and lumbar puncture with opening pressure measurement were unremarkable. Because the optic disc findings were persistent, she underwent examination under anesthesia with fluorescein angiography, which revealed bilateral neovascularization of the optic disc (NVD) with peripheral retinal non-perfusion. Systemic workup including hemoglobin A1C measurement was normal. She underwent four sessions of bilateral panretinal photocoagulation and three intravitreal injections of anti-vascular endothelial growth factor (VEGF) with subsequent improvement of the NVD in both eyes.

Conclusions and importance: Neovascularization of the optic disc may arise in Alström syndrome as a sequela of peripheral retinal ischemia. This finding may be partially responsive to panretinal photocoagulation and intravitreal anti-VEGF therapy.

1. Introduction

Alström syndrome is an autosomal recessive ciliopathy caused by variants in the *ALMS1* gene and is characterized by early-onset cone-rod dystrophy in addition to multiple systemic abnormalities.[1] The prevalence in the United States and Europe is estimated to be less than one per million.[1] Neovascularization in Alström syndrome is rare, and a single case of peripheral retinal ischemia with retinal telangiectasias and exudative retinopathy has been previously reported.[2] We present the first case, to our knowledge, of optic disc neovascularization in a patient with Alström syndrome.

2. Case report

A 3-year-old female was referred to the pediatric neuro-ophthalmology clinic due to poor vision and nystagmus, first noticed at the age of 10 months. She was seen by an outside ophthalmologist who prescribed glasses for high hyperopia and recommended further evaluation with genetic testing and an electroretinogram. The patient had global developmental delay and was non-verbal.

On exam, she was noted to have poor fixation with each eye and limited ability to follow faces. Pupils were reactive to light with no afferent pupillary defect. She had full ocular ductions and a sensory exotropia measuring 35 prism diopters by Krimsky testing. Conjugate, pendular, horizontal nystagmus was present. She was noted to be photophobic, and anterior segment and dilated fundus examinations appeared normal. Cycloplegic refraction in the right eye was +5.50 + 4.00x80 and in the left eye was +6.00 + 4.00x90.

Based on the exam findings, Leber congenital amaurosis (LCA) was suspected and she underwent an eye exam and electroretinography

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(ERG) under sedation. The fundus examination was notable for attenuated arterioles but normal appearing maculae and retinal periphery. The optic nerves were described as pink and crowded. The ERG revealed non-recordable scotopic and photopic responses in each eye. Scotopic responses were recorded after 20 minutes of dark adaptation.

The patient underwent whole genome sequencing by HudsonAlpha Clinical Services Lab, LLC (Huntsville, AL), using the Illumina HiSeq X sequencing platform. This demonstrated a homozygous nonsense variant in the *ALMS1* gene (NM_015120.4:c.4746C > G; p.Tyr1582Ter), which was validated by Sanger sequencing. This variant has not been previously reported in affected individuals and was absent from large population studies (gnomAD version 2.1.1).[3] The variant was classified as likely pathogenic according to joint American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) guidelines as it is a loss of function variant that is absent from controls (PVS1 and PM2 pathogenicity criteria),[4] which led to a diagnosis of Alström syndrome. Genome sequencing did not reveal a potential alternate explanation for this individual's clinical presentation. Trio sequencing revealed that both parents, who were unaffected, were heterozygous for this variant, which is consistent with an autosomal recessive model of inheritance. She was evaluated by a geneticist and was found to have hearing loss and obesity, but no other systemic complications typically associated with Alström syndrome such as diabetes, cardiomyopathy, pulmonary, hepatic, or renal dysfunction.

For three years, the patient was monitored by an outside ophthalmologist with stable vision. She returned to our pediatric neuro-ophthalmology clinic for a routine exam at the age of six years with no new ocular complaints, but report of chronic headaches. Her visual acuity and oculomotor exam were unchanged. However, on dilated fundus examination, her optic nerves were noted to be hyperemic and appeared swollen. Due to concern for papilledema, she was admitted for brain and orbital magnetic resonance imaging (MRI) followed by lumbar puncture. The MRI scan was unremarkable, and the lumbar puncture demonstrated an opening pressure of 21 cm H_2O with normal CSF constituents. The differential diagnosis included resolving papilledema or papillitis. Since her visual acuity remained unchanged, the decision was made to observe closely without treatment.

After two months of observation, the optic nerve appearance remained unchanged. Due to poor cooperation, an eye examination under anesthesia was performed. This demonstrated normal intraocular pressures and anterior segments bilaterally. However, funduscopic examination revealed apparently swollen optic discs bilaterally with hyperemia and abnormal, tortuous vessels lying on the peripapillary retina (Fig. 1). There were no visible optic disc drusen. Both eyes featured blunted foveal reflexes, retinal vascular attenuation, and peripheral pigmentary retinopathy. In addition, there was scant vitreous hemorrhage inferiorly in the right eye. Intraoperative hand-held optical coherence tomography (OCT) of the maculae showed attenuated ellipsoid zone in both eyes indicative of photoreceptor loss, consistent with retinal degeneration. Fluorescein angiography (FA) demonstrated late leakage of the optic discs and peripapillary abnormal vessels (consistent with neovascularization of the disc [NVD]), as well as diffuse late capillary leakage in a fern-like distribution. There was marked peripheral retinal non-perfusion as well (Fig. 2). Laboratory studies were drawn to evaluate for diabetes and inflammatory and infectious causes of retinal vascular disease. Laboratory work-up revealed hemoglobin A1C of 5.6, erythrocyte sedimentation rate (ESR) of 17, normal blood cell counts and electrolytes, normal angiotensin converting enzyme (ACE), non-reactive rapid plasma reagin (RPR), and negative antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and double-stranded DNA (dsDNA).

Subsequent review of fundus photographs obtained three years previously at the time of sedated ERG showed that abnormal vessels on the optic disc were present bilaterally, although less prominent and not appreciated at that time (Fig. 3).

Because significant peripheral retinal non-perfusion was present, four sessions of panretinal photocoagulation to the avascular periphery were performed, in addition to three intravitreal injections of bevacizumab over 15 months. At the end of treatment, the vitreous hemorrhage resolved in both eyes and the NVD was persistent but improved (Fig. 4), with decreased leakage on FA (Fig. 5). The optic discs were flat and the borders were sharp, and there was no evidence of buried or superficial optic disc drusen.

3. Discussion

Alström syndrome can present with a variety of systemic manifestations including cone-rod dystrophy, sensorineural hearing loss, obesity, type 2 diabetes mellitus, cardiomyopathy, and pulmonary, hepatic, and renal dysfunction with multi-organ fibrosis.[1] Ophthalmic and cardiac findings are typically the first manifestations, usually developing in infancy.[5] Infantile cardiomyopathy, which was not diagnosed in our patient, has been reported in 42% of children with Alström syndrome.[5] Sensorineural deafness is diagnosed in 70% of patients before 10 years of age.[5] Most patients develop childhood obesity, which typically begins within the first two years of life.[6] Type 2 diabetes mellitus,

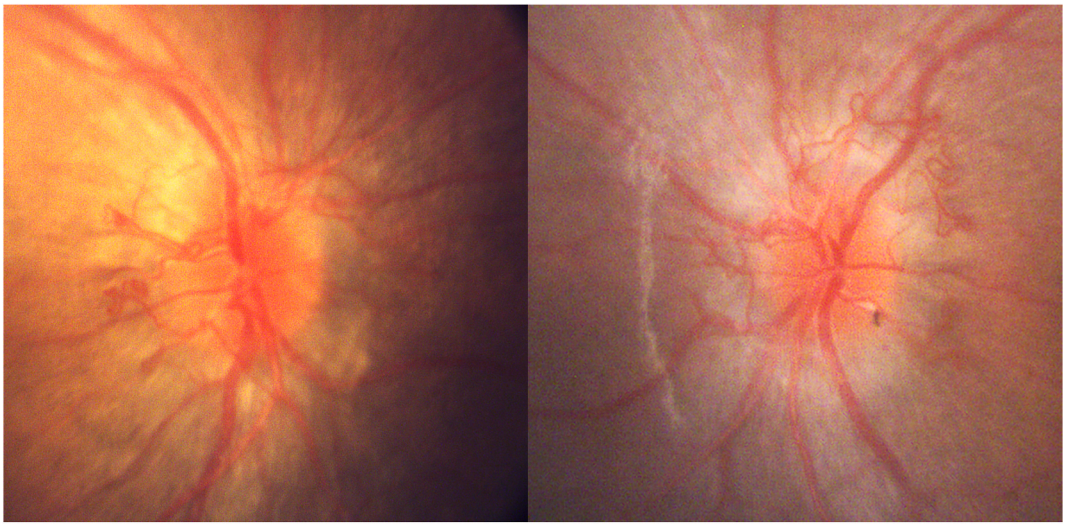

Fig. 1. Fundus photographs of the right and left optic discs, demonstrating hyperemia and apparent swelling, with abnormal, tortuous vessels consistent with neovascularization of the disc (NVD).

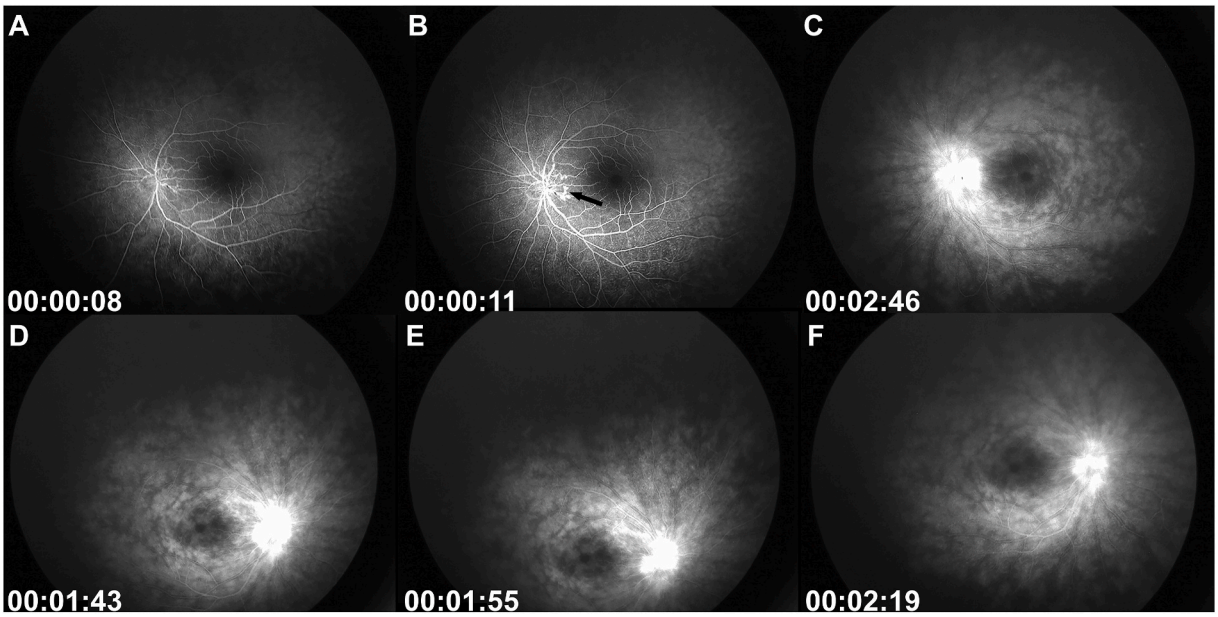

Fig. 2. A-C. Fluorescein angiography (FA) of the left eye showing leakage of telangiectatic vessels on the optic disc (arrow), consistent with neovascularization. D-F. Late-phase FA of the right eye demonstrating optic disc leakage and peripheral retinal non-perfusion.

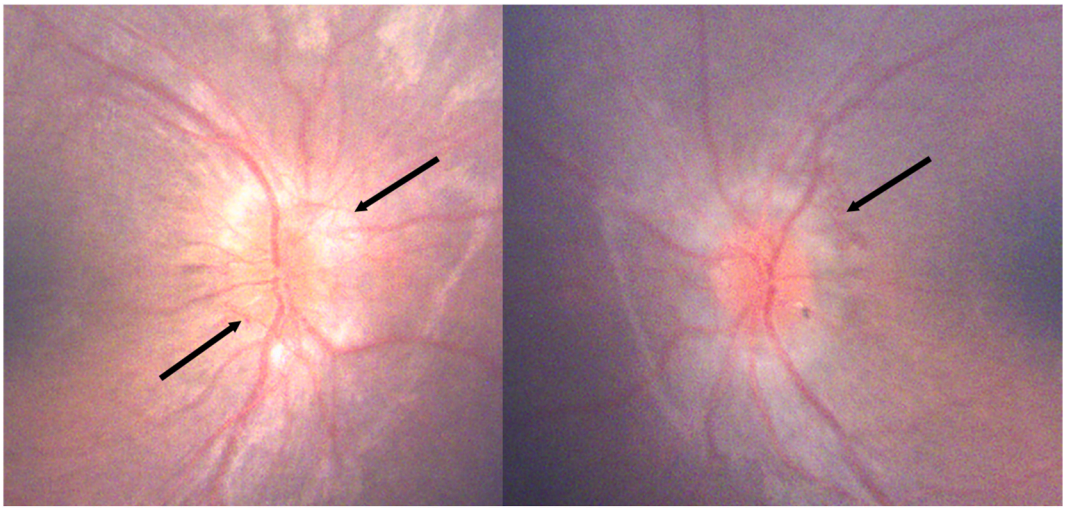

Fig. 3. Fundus photographs of the right and left optic discs taken three years prior to treatment. Neovascularization of the disc (arrows) is present in both eyes, but there are fewer abnormal vessels than in Fig. 1.

which eventually affects 82% of patients with Alström syndrome, has a reported median age of onset of 16 years.[5] Thus, our patient's symptoms of cone-rod dystrophy, childhood obesity, and hearing loss without diabetes mellitus at 6 years of age are consistent with prior reports, although she does not completely match the classic description of Alström syndrome due to the absence of infantile cardiomyopathy.

Retinal dystrophy is the most consistent feature of Alström syndrome, with a reported incidence of 100%.[5] Patients present with nystagmus, poor vision, and photophobia with high hyperopia in infancy.[7] Initial ERG shows diminished cone response, followed later by decreased rod function, consistent with a cone-rod dystrophy.[8] Differential diagnosis includes Leber congenital amaurosis, achromatopsia, isolated cone-rod dystrophy, and Bardet-Biedl syndrome.[7]

Other ocular characteristics of Alström syndrome include optic disc pallor, optic disc drusen, attenuation of retinal vessels, macular pigmentary changes, and atrophic retinal pigment epithelium (RPE) without bone spicules.[7] To our knowledge, optic disc neovascularization has not been described in association with Alström syndrome.

Among patients with other inherited retinal dystrophies, such as retinitis pigmentosa (RP), a few cases of NVD have been reported.[9–11] The pathophysiology may relate to retinal vascular attenuation. Although the stimulus for vascular narrowing is believed to be hyperoxia caused by the retinal degeneration, in rare cases the vasculature may become over-attenuated, leading to hypoxia and subsequent neovascular response.[10] We believe the mechanism of NVD in our patient with Alström syndrome is similar to these cases, since we observed retinal vascular attenuation, retinal degeneration on OCT, and peripheral retinal non-perfusion on FA.

Prior cases of NVD in patients with RP were treated with panretinal photocoagulation or cryotherapy, except for one patient who underwent sub-Tenon's triamcinolone injection.[9–11] We opted to treat with panretinal photocoagulation under anesthesia followed by intravitreal anti-vascular endothelial growth factor (VEGF) when persistent NVD was observed. Although the NVD improved with treatment, some

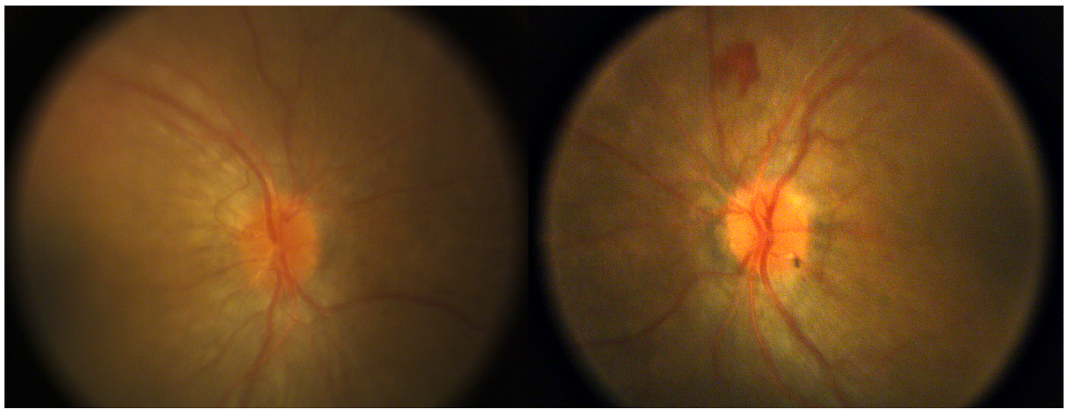

Fig. 4. Fundus photographs of the right and left optic disc after treatment with panretinal photocoagulation and intravitreal bevacizumab injections. The neovascularization of the disc (NVD) is still present, but improved compared to Fig. 1.

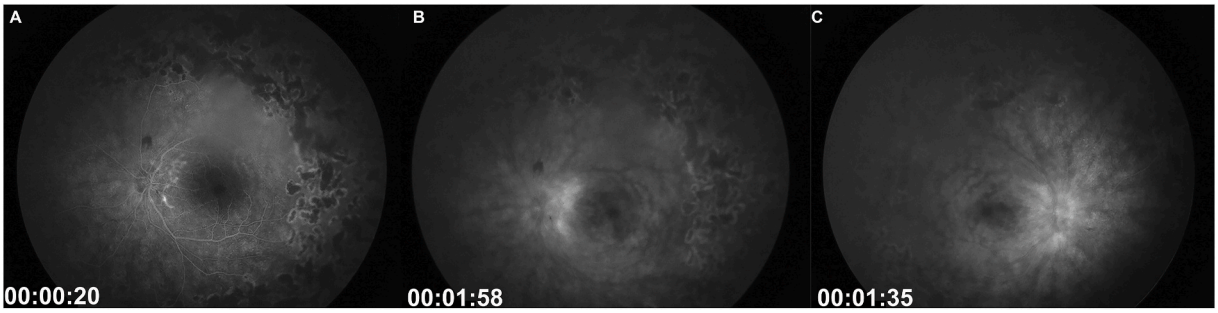

Fig. 5. Fluorescein angiography (FA) of the left eye, early (A) and late (B), and right eye, late (C). The leakage from the neovascular vessels has decreased compared to Fig. 2.

abnormal vessels did not regress and continued to leak on FA. Partial treatment resistance could be related to chronic vascular alterations, since the NVD was present for at least three years before treatment.

It is unclear why our patient had optic disc swelling. One possibility is a VEGF-mediated ischemic papillopathy, similar to patients with diabetic papillopathy, which may occur simultaneously with NVD.[12] Another possible explanation is an inflammatory papillitis, which we consider less likely due to the presence of vitreous hemorrhage without vitritis. We considered a trial of topical steroids but decided against this because of her inability to cooperate with intraocular pressure monitoring in clinic.

Our patient was homozygous for a novel nonsense variant (NM_015120.4:c.4746C > G; p.Tyr1582Ter) in the *ALMS1* gene. Since this is a single case report, we cannot confirm whether the finding of NVD represents a unique phenotypic manifestation of this particular mutation. In general, poor genotype-phenotype correlation has been observed in patients with Alström syndrome.[13]

4. Conclusions

Cone-rod dystrophy is the typical ophthalmic manifestation of Alström syndrome. The optic nerve can appear atrophic and contain optic disc drusen. Our case demonstrates that optic disc neovascularization may also occur, presumably due to retinal vascular attenuation and peripheral retinal ischemia. The neovascularization may require multiple rounds of treatment with laser photocoagulation and intravitreal anti-VEGF agents, and may be partially treatment resistant. Ophthalmologists should be aware of this rare potential complication of Alström syndrome and monitor and treat patients accordingly.

Patient consent

The patient's legal guardian consented to the publication of the case report in written form.

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Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: MYC, MSB. AN serves as a consultant for Allergan Retina, Novartis, Regenxbio, and Biogen.

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