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Ocular findings associated with FADD deficiency resemble familial exudative vitreoretinopathy

Elana Meer [a], Federica Solanes [b], Lisa Kohn [c], Caroline Y. Kuo [c], Derek A. Wong [d], Stacy Pineles [b], Irena Tsui [b,*]

[a] University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[b] Stein Eye Institute, Department of Ophthalmology, UCLA, USA
[c] Pediatric Allergy and Immunology, Department of Pediatrics, UCLA, USA
[d] Genetics, Department of Pediatrics, UCLA, USA

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ABSTRACT

Purpose: We report the first known case of eye findings associated with a Fas-associated protein with death domain (FADD) gene mutation, an exceedingly rare entity.

Observations: A 7-year-old boy was referred for decreased vision and eye examination revealed cystoid macular edema and peripheral retinal ischemia in both eyes and progression to tractional retinal detachment in the right eye.

Conclusions and Importance: This case suggests that baseline and annual ophthalmic screening may be beneficial in individuals with FADD mutations. However, greater documentation of cases may be necessary before deriving a clear interval screening recommendation.

1. Introduction

Fas-associated protein with death domain (FADD) deficiency is a rare and severe genetic mutation characterized by recurrent infections, encephalopathy, cardiac abnormalities, and short life expectancy. FADD, a novel death domain-containing protein located on the long arm of chromosome 11 (11q13.3), plays an important role in programmed cell death, a physiologic process essential to the normal development and homeostatic maintenance of multicellular organisms, as well as to cell proliferation, embryogenesis, and immune regulation.[3]

There are only three families in reported in the literature, including the one we are describing. The purpose of this report is to describe novel eye findings associated with a FADD gene mutation.

2. Case report

A 7-year-old boy with compound heterozygous FADD gene mutations was referred to ophthalmology for acute visual loss in his right eye. Whole exome sequencing was previously performed and demonstrated two heterozygous FADD gene mutations in trans, c.52_58delAGCGAGC and c.313T > C, inherited from his mother and father respectively.[6]

The patient was born full term to non-consanguineous parents with an uncomplicated prenatal and postnatal course. At 14 months old he presented with diarrhea, fever and vomiting with secondary dehydration. During this hospital admission, he had a tonic-clonic seizure episode and given a family history of an older brother who died at the age of 18 months with status epilepticus, possible sepsis and multi-organ failure with no known diagnosis, the patient underwent systemic and genetic evaluation. As part of genetic evaluation, he had an ophthalmologic exam by a pediatric ophthalmologist at 15 months (portable slit lamp exam, dilated fundus exam, pressure, motility), which demonstrated no abnormalities. A summary of the patient's medical history is presented in Table 1. The patient had elevated Fas-ligand levels, with a decreased percentage of apoptosis seen on fas-mediated apoptosis testing (2%), high number of double negative T cells and elevated IL-10 level, biological features of autoimmune lymphoproliferative disorder (ALPS). Despite the presence of a spleen, Howell-Jolly Bodies were present in the blood smear, evidence of impaired splenic phagocyte function. He also demonstrated low antibody response to isohemagglutinins thought to be due a functional defect from the FADD mutation. In addition, physical exam was notable for hepatomegaly with a cholestatic picture of elevated LFTs at 15 months, which improved to a

* Corresponding author. 100 Stein Plaza, Los Angeles, CA, 90095, USA
E-mail address: itsui@jsei.ucla.edu (I. Tsui).

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mild persistent hepatomegaly (Table 1) The patient's glucose and electrolytes were largely normal. White count was normal, though platelets were a bit low (~110) and with anemia (Hgb 9.8). A lumbar puncture was performed with 3WBC, 1RBC < glucose 59, but with protein 318. Genetic testing included exome sequencing to cover seizure genes, coagulation genes (For stroke risk), polymerase gamma, as well as mitochondrial liver disease, with FADD mutations as specified above.

The patient presented to ophthalmology at 7 years old with acute vision loss. Ophthalmologic exam revealed visual acuity of 20/400 in the right eye and 20/60 in the left eye (Table 2). Anterior segment exam was unremarkable and dilated fundus exam showed neovascularization of the optic disc with a tractional retinal detachment and associated vitreous hemorrhage in the right eye (Fig. 1), bilateral peripheral retina ischemia (Fig. 1), and bilateral cystoid macular edema (CME) (Fig. 2). The left eye did not have retinal vitreous hemorrhage or retinal detachment.

The patient underwent an exam under anesthesia with targeted retinal photocoagulation in both eyes and an injection of anti-vascular endothelial growth factor (ranibizumab 0.25 mg/.05 cc) in the left eye, supplemented by nepafenac twice daily, with stabilization of symptoms. Patient was lost to follow-up for 5 months due to COVID-19. When he represented, vision was stable (20/400 in the right eye and 20/70 in the left eye), and CME in his left eye had improved (Fig. 3). The patient was recommended to undergo pars plana vitrectomy in the right eye for vitreous hemorrhage and tractional retinal detachment. The patient was lost to follow-up due to an extended outside hospitalization for neurological issues. At the most recent follow-up, 1 year after his EUA/laser/injection, vision was HM in the right eye, 20/60 in the left

Table 2
Ophthalmologic findings in patient.

	OD	OS
Visual Acuity	20/400 + 1	20/60-2
Tonometry	normal	normal
Pupillary Reflex	normal	normal
Visual Fields	normal	normal
Slit Lamp exam	normal	normal
Motility	normal	normal
Alignment	normal	normal
Cycloplegic Refraction	+0.50 + 1.00x90°	plano+1.50x90°
Fundus Exam (Fig. 1)	Neovascularization of the optic nerve with tractional retinal detachment and associated vitreous hemorrhage + cystoid macular edema	Cystoid Macular Edema
Wide Field Fluorescein Angiography (Fig. 2)	Peripheral Retinal Ischemia and Neovascularization	Peripheral Retinal Ischemia and Neovascularization
Macular OCT (Fig. 3)	Cystoid Macular Edema with central subretinal Fluid	Cystoid Macular Edema with central subretinal Fluid
B-Scan (Fig. 4)	Clusters of dense opacities anteriorly with a vitreous membrane and peri-papillary vitreoretinal adhesions	Deferred (retina attached)

Table 1
Comparative Clinical Presentations of Patients with FADD deficiency.

	Bolze (2010)	Savic et al.(2015)	This Case	
			Patient	Patient's Brother
Mutation	c.315T > G homozygous	c.315T > G; p.C105W homozygous	c.52_58delAGCGAGC, c.313T > C compound heterozygous	
Gender	1 male, 3 female	2 female, 2 male	Male	Male
Cardiovascular malformation	Pulmonary atresia + VSD, L sided SVC draining to left atrium	Presence of congenital cardiac abnormalities	Echocardiogram was previously performed and found to be normal	
Functional hypoesplenism	Spleen size normal Howell –Jolly bodies present Invasive pneumococcal infection (meningitis, septicemia)	Suboptimal anti-pneumococcal antibody titers despite repeated Prevnar 13 vaccination	Howell-jolly bodies present Invasive pneumococcal infections Advice for vaccines and prophylactic antibiotic. IgG replacement initated.	
Features of febrile episodes	Documented viral trigger (VZV, HHV6, MMR vaccine, astrovirus, parainfluenza 2, EBV) Encephalopathy Seizures Liver dysfunction (maximal ALT 1042)	Documented Recurrent viral Infections, encephalopathy and seizures, pneumococcal meningitis	Documented recurrent infections, encephalopathy, seizures	Trigged by MMR vaccine vaccine Encephalopathy Seizures Liver Dysfunction Recurrent Infections Rashes
APLS phenotype	Autoimmune disease Autoantibodies to antierythrocyte intermittently x1 Impaired lymphocyte apoptosis x 1 Serum FasL, serum IL10 elevated x1	Normal Immunoglobulin profile and complement studies Negative autoimmune screen Marginla elevation in Cd4-Cd8- T cells	No autoimmunity - demonstrates low antibody response to isohemagglutinins Elevated CD4-CD8- TCR T cells Lymphocyte apoptosis decreased Elevated Serum FasL, IL10	
CNS	Neurodevelopmental progress Cerebral atrophy (3–5 months) x3		Speech delay MRI showed restricted diffusion of the white matter of the corpus collosum	
Ophthalmology			Peripheral retinal ischemia, neovascularization, vitreal hemorrhage, retinal detachment, CME	
Liver	Mild chronic portal inflammation with bridging fibrosis, elevated ALT	Mild liver dysfunction (ALT 76)	Hepatomegaly LFTS were elevated Alk phos (165), ALT (40) at 15, which improved to mild persistent hepatomegaly at most recent presentation	
Follow up data	(1) Died at 4 months (2) Died at 14 months (3) Died at 4 years 4 months (4) Alive at 2 years 9 months in 2010 without further follow up data	(1) Died in infancy (2) Died in infancy (3) Died at 4 months (4) Alive at 3 years old in 2015 without further follow up data	(1) Alive at 8 years	(1) Died at 18 months

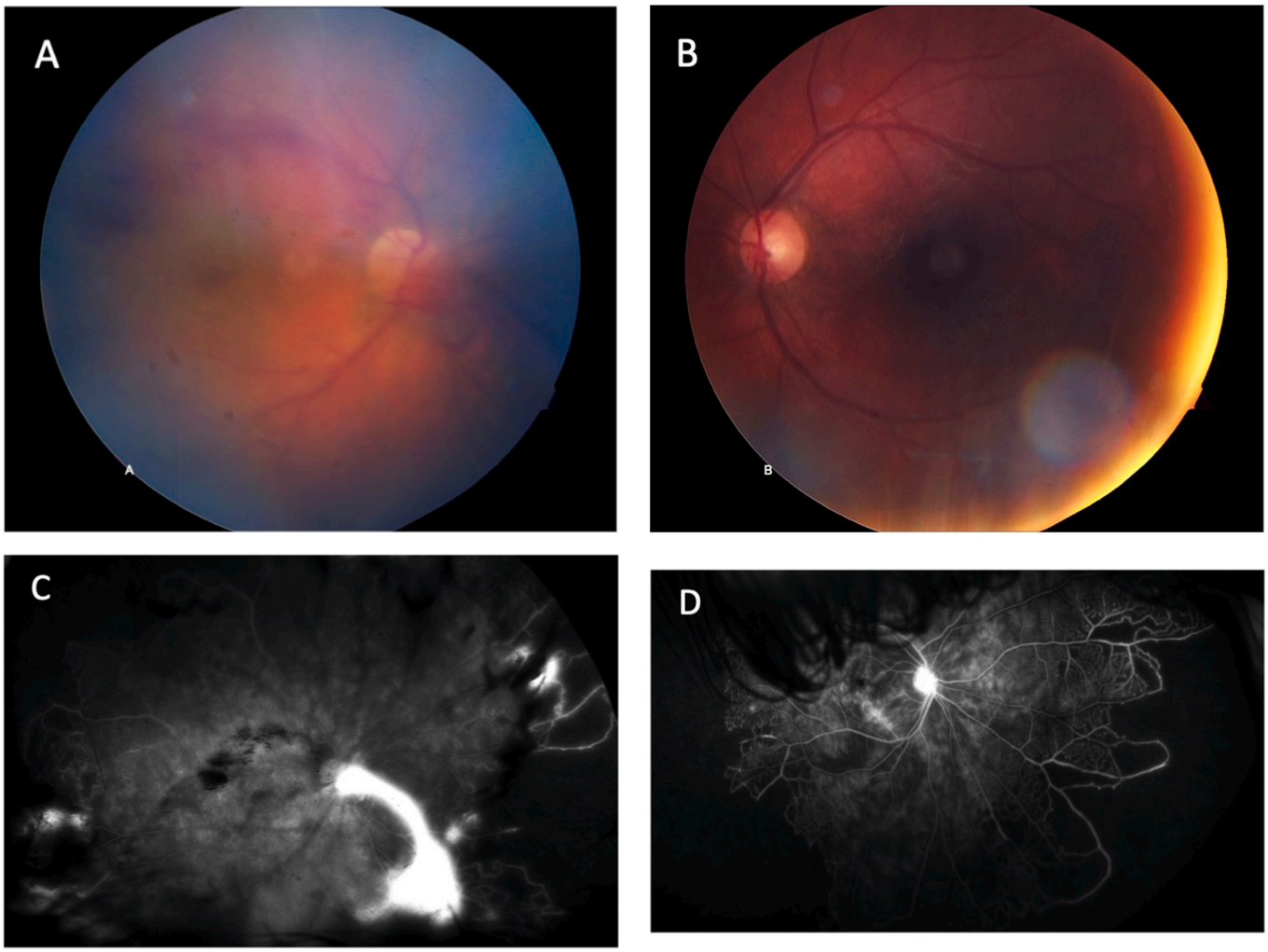

Fig. 1. Color photos of optic nerve and macula (Optos) and Fluoroscein Angiogram (FA) **A.** Color fundus photograph of right optic nerve with hyperemia of the infranasal optic nerve, vitreous hemorrhage and neovascularization of the disc. **B.** Color fundus photograph of left optic nerve without neovascularization. **C.** Late FA of Right Eye with peripheral retinal avascularity and peripheral retinal and macular leakage. **D.** Late FA of Left eye with peripheral retinal avascularity and peripheral retinal and macular leakage.. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

eye. The vitreous hemorrhage in the right eye had worsened with no view to the back. B-scan of the right eye showed stable tractional retinal detachment. The left eye was stable with improved CME and good laser treatment with peripheral laser (Fig. 4). Pars plana vitrectomy was recommended in his right eye and is pending pre-operative clearance. The left eye had notable neovascularization of the disc without neovascularization seen in the retina periphery and resolved CME on OCT. The patient will have additional laser and anti-VEGF injection in the left eye at the time of right eye surgery.

3. Discussion

In this report, we present a 7-year-old boy with FADD deficiency (MIM 613759), the oldest reported patient with this disease. The patient had systemic manifestations similar to previously reported families, namely recurrent febrile episodes, encephalopathy, seizures, lymphadenopathy/splenomegaly (Table 1).[1] There are no prior eye findings reported with FADD deficiency, likely because it is exceedingly rare with a short life expectancy and visual dysfunction is confounded by severe neurological dysfunction.

This patient presented with CME and peripheral retina ischemia in both eyes and a tractional retinal detachment in one eye. This presentation is similar to familial exudative vitreoretinopathy (FEVR), an inherited disorder of retinal angiogenesis with variable expressivity.[2] Although variable, clinical presentation of FEVR is classically isolated to the eye, and involves peripheral retinal ischemia, pre-retinal vascularization and fibrosis with CME as seen in this case.,[2]Genetic analysis in this patient demonstrated FADD deficiency without mutations identified in known FEVR genes. While the importance of this case from an immunologic standpoint has been reported in the literature,[7] this report uniquely discusses the ophthalmologic manifestations and management.

FADD, a novel death domain-containing protein located on the long arm of chromosome 11 (11q13.3), plays an important role in programmed cell death, a physiologic process essential to the normal development and homeostatic maintenance of multicellular organisms, as well as to cell proliferation, embryogenesis, and immune regulation.[3] Signal transduction mediated by FADD represents a paradigm of co-regulation of apoptosis and cellular proliferation. FADD is involved in the early signal transduction process that allows for the TNF alpha-FAS-FADD complex to lead to caspase activation and ensuing apoptosis.[3] Mutations in FADD abolish its ability to bind the domains of Fas and TNFR-1 and subsequently activate caspase 8 responsible for triggering cell death.[8] Therefore, as a crucial regulator of life and death of certain cells, FADD deficiency has many systemic findings, manifesting with recurrent febrile episodes, encephalopathy, seizures, variable degrees of lymphadenopathy or splenomegaly, cerebral atrophy,

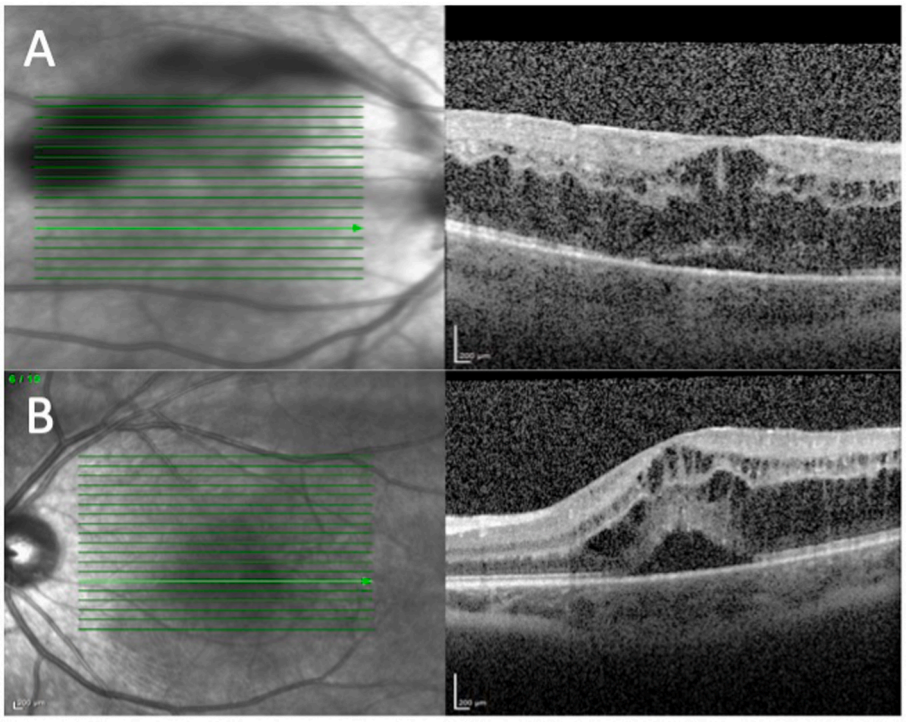

Fig. 2. OCT demonstrating diffuse cystoid macular edema (CME) with central subretinal fluid in both right (**A**) and left (**B**) eyes.

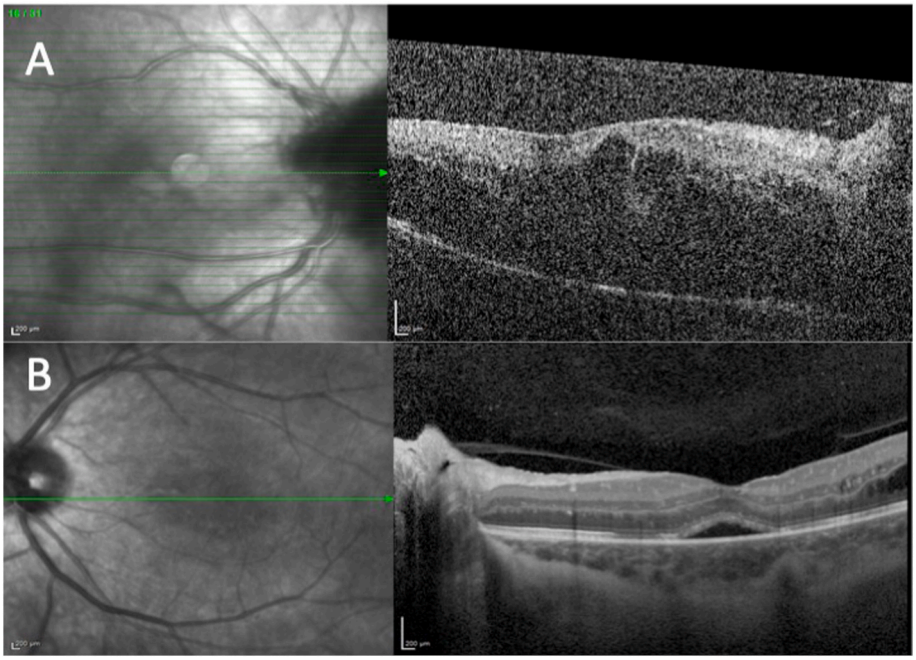

Fig. 3. Optical coherence Tomography at 5 months follow up in both right **(A)** and left (**B**) eyes. OCT demonstrates improvement in CME after a single ranibizumab injection and targeted retinal laser photocoagulation therapy in left eye.

and structural cardiac abnormalities.[9]

The phenotypic similarities between FEVR, an inherited disorder of retinal angiogenesis, and the ocular findings in this patient with FADD deficiency may be explained by their shared pathway, as well as adjacent gene locus on chromosome 11.13, leading to altered caspase 8 activity and downregulation of apoptosis.[2,4] TNF-alpha, the initiator of the caspase activating cascade, has been shown to contribute to ischemic retinopathy as elevated expression is associated with increased upstream activation of FAS-FADD-caspase activation and ischemic neuronal injury.[5] We hypothesize that dysfunction of this cascade may lead to continuous inflammation in the retina secondary to endothelial dysfunction, and ensuing retinal ischemia with reactive neovascularization similar to FEVR.[3,5] It is also possible that the peripheral retina ischemia was more a manifestation of vaso-obliteration or an associated developmental abnormality in which the vessels did not make it out all the way to the periphery of the retina in utero. Furthermore, compensatory overexpression of TNF alpha, the initiator of the cascade may modulate ion channel activity causing excitotoxic injury to retinal

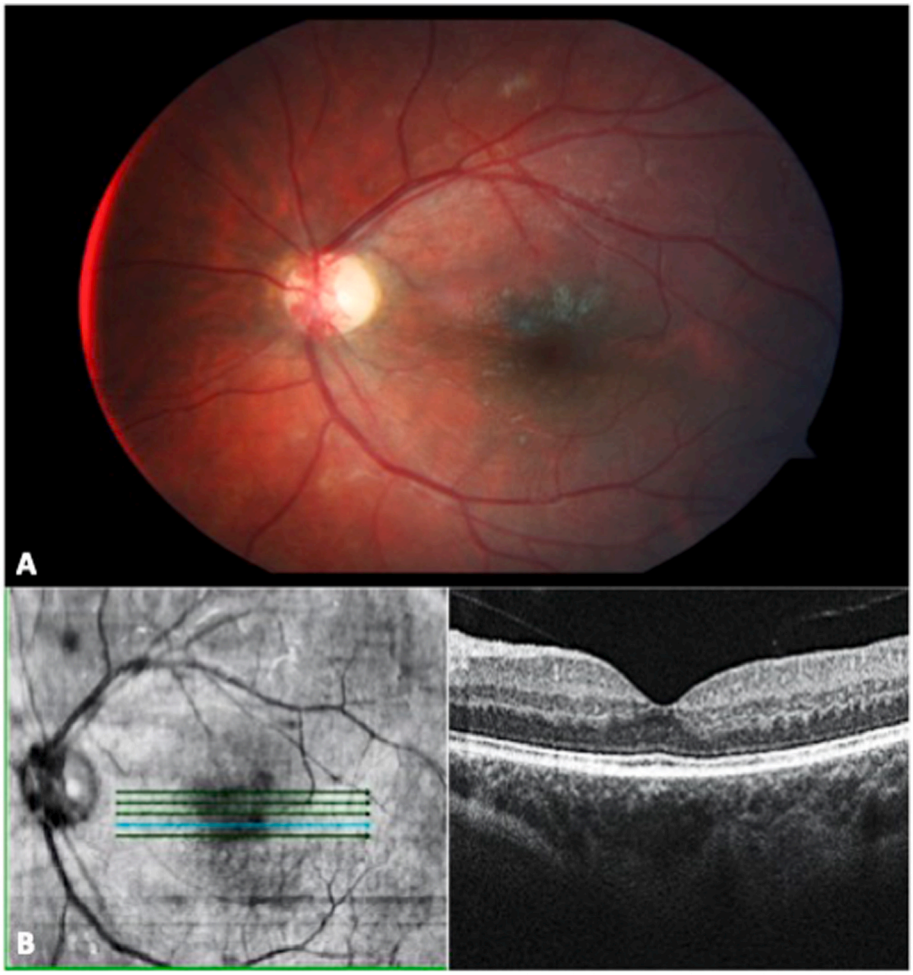

Fig. 4. Color Photo and Optical Coherence Tomography at 1 year follow up in left eye. **A.** Color fundus photograph of left optic nerve with extensive neovascularization of the disc**. B.** OCT of the left eye demonstrates resolution of CME. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ganglion cells in the retina, and independently induce angiogenesis through increasing vascular permeability and VEGF secretion.[5] It is also important to note that FEVR is phenotypically and genotypically variable, and not all contributory genes and mutations are known. Therefore, while the pathophysiology of a FADD mutation is in line with the clinical presentation as described, it is still difficult to completely rule out FEVR as a separate diagnosis in this case.

4. Conclusions

In summary, this case heralds the ophthalmic manifestations of FADD deficiency. Currently there have been only two other known families with FADD mutations reported in the literature, both consanguineous.[1,6] The significance of our patient's genetic mutations and systemic manifestations has been previously reported,[7] however, we give further importance to the common role of the TNF alpha-FAS-FADD-caspase8/3 programmed cell death pathway in sustaining systemic immune and retinal cells.[2] Baseline and annual ophthalmic screening may be beneficial in individuals with FADD mutations. However, greater documentation of cases may be necessary before deriving a clear interval screening recommendation.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

Appendices

None.

Declaration of competing interest

None of the authors have financial disclosures

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