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Early Onset Neovascular Inflammatory Vitreoretinopathy Due to a *De Novo* CAPN5 Mutation: Report of a Case

Ghazala O’Keefe, MD¹, Adam M. Hanif, BA¹, Vinit B. Mahajan, MD^{2,3}, Nieraj Jain, MD¹

¹Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, USA

²Byers Eye Institute, Omics Laboratory, Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, CA, USA

³Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Abstract

Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is a rare autoimmune condition that typically presents as progressive uveitis and vitreoretinal degeneration between the second and third decades of life. Though traditionally attributed to inherited mutations of the CAPN5 gene, few reports of de novo variants exist. This report of vision and hearing loss in a 3 year-old girl describes the youngest documented case of ADNIV due to a de novo pathogenic c.865C>T (p.Arg289Trp) CAPN5 variant, illustrating the early stages of this enigmatic disease process.

Keywords

ADNIV; calpain; CAPN5; uveitis

To the Editor,

We wish to inform your readers of a unique case of early-onset autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV), a rare autoimmune condition that traditionally manifests between the second and third decades. In this letter, we describe a three-year-old female with bilateral dense cataracts, panuveitis, and retinal degeneration. To our knowledge, this describes the youngest documented case of ADNIV, attributable to a *de novo* CAPN5 mutation.

A 3-year-old Caucasian female presented with a history of several months of panuveitis and white cataracts in both eyes. Her parents reported her having visual difficulties in adequate lighting, and timidity when approaching steps or transitions in flooring since two years of age. They denied other focal neurological symptoms. Examination under anesthesia performed at an outside facility revealed diffuse vascular leakage, fluid in Tenon’s space, and diffuse choroidal thickening. She subsequently underwent cataract extraction,

Correspondence: Nieraj Jain, MD, 1365B Clifton Road NE, Suite 2400, Atlanta, GA 30322. nieraj.jain@emory.edu.

DECLARATION OF INTEREST

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intraocular lens implantation, and perioperative subtenons triamcinolone acetonide injection, yielding visual improvement. At that time, extensive laboratory workup showed an elevated c-reactive protein (6.2) and Bartonella IgG (1:512) titers, for which she completed a course of combination antibiotic therapy and oral prednisone.

Best-corrected visual acuity (BCVA) at presentation to our clinic was count-fingers at 2 ft. bilaterally. Slit lamp exam was significant for mild peripheral band keratopathy and rare anterior chamber cell in both eyes. Dilated fundus examination revealed 1+ anterior vitreous cell and attenuated arterioles. Fluorescein angiography revealed mild disk leakage without petaloid macular leakage, vasculitis or peripheral nonperfusion (Figure 1, A–B). Optical coherence tomography revealed fovea-sparing outer retinal atrophy, thickened inner retinal laminations, and cystoid macular edema bilaterally. Fundus autofluorescence imaging demonstrated a subtle parafoveal hyperautofluorescent ring (Figure 1, C–D).

Molecular testing with a next-generation sequencing panel-based approach revealed several variants, including the deleterious c.865C>T (p. Arg289Trp) variant in *CAPN5*. Other variants did not match the phenotype or mode of inheritance. Further testing revealed that neither parent harbored this variant in *CAPN5*. This finding was consistent with autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV, OMIM #193235) due to a *de novo* mutation. On the basis of prior reports of hearing loss associated with this variant, our patient underwent a full audiometry evaluation. Conditioned play audiometry revealed mild sensorineural hearing loss at 2000 Hz bilaterally. Tympanometry was consistent with normal middle ear function in both ears.

Although other ADNIV patients failed anti-TNF α therapy, our patient appears stable on infliximab, methotrexate, and topical prednisolone, with trace residual anterior chamber cells in the left eye and persistent CME bilaterally.¹ She did not tolerate a brief course of topical dorzolamide. BCVA improved to 20/125 and 20/150 in the right and left eyes at the age of 4.

ADNIV is a rare autoimmune disorder characterized by uveitis and vitreoretinal degeneration that typically presents between the second and third decades of life.² Heralded by uveitis, the condition progresses to retinal degeneration and peripheral retinal neovascularization. Fibrosis, tractional retinal detachment, and blindness ultimately develop typically by the fifth decade.² ADNIV is caused by mutations in *CAPN5*, which encodes a calcium-activated cysteine protease expressed in the retina. Pathogenic *CAPN5* mutations lead to loss of calcium regulation and hyperactivation of protease activity.^{3,4}

Here we present and characterize the youngest documented case of ADNIV due to a *de novo* mutation of the *CAPN5* gene. In this unique case, a constellation of clinical findings suggested a diagnosis of ADNIV, and the identification of a disease-causing *de novo* mutation in *CAPN5* corroborated our clinical suspicion. Briefly, our patient presented with bilateral panuveitis as well as characteristic findings of a hereditary retinal degeneration, including perifoveal atrophy of the outer retina, atypical inner retinal laminations, and a hyperautofluorescent parafoveal ring.

De novo p.Arg289Trp mutations in *CAPN5* have been twice reported, describing the progressive sensorineural hearing loss and ocular findings including anterior and posterior inflammatory cells, cataracts and retinal membranes progressing to endstage uveitis.^{3,5} Interestingly, these patients presented at 9 and 10 years of age, demonstrating that this particular genotype is associated with an early-onset disease. The earlier onset and increased disease severity associated with the p.Arg289Trp mutation correlates with greater *CAPN5* hyperactivity due to stabilization of the mutant calpain in its active conformation.³ These findings suggest that children with posterior uveitis and vitreoretinopathy may benefit from genetic testing even without a family history of disease.

Although uveitis is a common cause of visual impairment, variable disease presentation undermines controlled study of novel therapies. ADNIV is, therefore, a growing topic of interest to investigators searching for a uveitis model with an identical gene defect, and a reliable phenotype confined to the eye.¹ Expanded understanding and documentation of this condition will permit advancements in the study of uveitis and development of novel therapies.

Respectfully,

Ghazala O'Keefe, Adam Hanif, Vinit Mahajan, and Nieraj Jain

Department of Ophthalmology

Emory University School of Medicine

1365B Clifton Road NE, Suite 2400

Atlanta, GA 30322

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FIGURE 1.

Multimodal ophthalmic imaging. **A.** Color fundus photograph of left eye, demonstrating moderate arteriolar attenuation. There was no peripheral pigmentary changes or neovascularization. **B.** Venous phase fluorescein angiogram demonstrating normal retinal perfusion without petalloid leakage, evidence of retinal vasculitis, or notable capillary nonperfusion. Findings were comparable between eyes. **C.** OCT of the right eye demonstrating outer retinal atrophy with relative sparing of the fovea, cystoid macular edema, and thick, poorly defined inner-retinal laminations. **D.** Fundus autofluorescence image of the right eye, demonstrating a subtle macular hyperautofluorescent ring and grossly intact peripheral autofluorescence.