A Young Patient with Vitreous Hemorrhage and Bilateral Arteriolar Tortuosity

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A 35-year-old Caucasian woman presented to The Retina Institute complaining of acute onset of transient floaters in her right eye peripheral visual field. She denied any complaints in her left eye. She reported an episode two years prior of floaters and decreased vision in the same eye which prompted her to visit an ophthalmologist who diagnosed a vitreous hemorrhage. No additional testing or intervention was performed and the patient reported spontaneous improvement. The patient denied any previous ocular trauma.

She reported chronic, infrequent migraines without ocular aura with the last episode several months prior to presentation. She denied any other systemic symptoms, denied having any known medical problems and denied taking any medications. She denied tobacco use and history of illicit drug use. She did report that she was undergoing genetic testing to assist with a diagnosis for family members. Her family history was remarkable for a father with early onset cerebrovascular accident in his 50's and a younger brother with a cerebrovascular accident at age 30.

On examination, corrected visual acuity was 20/20 in the right eye and 20/40 in the left eye, presumably due to lifelong mild refractive amblyopia. Intraocular pressures were normal OU, no relative afferent pupillary defect was noted and ocular motility was normal. Visual fields were full to confrontation and subsequent 24-2 Humphrey visual fields confirmed no abnormalities.

Anterior segment examination was unremarkable and showed normal conjunctival vessels and no rubeosis in either eye. Fundus exam revealed minimal hemorrhage in the inferior vitreous cavity of the right eye and clear vitreous in the left eye. Optic nerves were pink and sharp with no disc neovascularization. Macular examination was unremarkable and OCT demonstrated normal contour (Figure 1). Retinal arterioles were tortuous, as seen on color photographs and red-free photographs, but the retinal venules were not dilated or tortuous (Figure 2). No peripheral retinal abnormalities were noted. Fluorescein angiography was performed with normal filling and transit time and no evidence of retinal vasculitis or neovascularization (Figure 3).

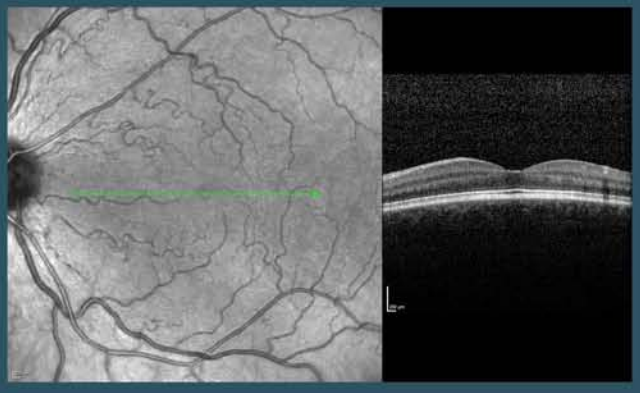


Figure 1

In summary, this young healthy patient had evidence of old vitreous hemorrhage in her right eye and bilateral retinal arteriolar tortuosity. The differential diagnosis included common entities: neovascularization from diabetic retinopathy, vein occlusion or sickle cell retinopathy; ruptured macroaneurysm, as well as vitreous hemorrhage as result of posterior vitreous detachment and/or retinal tear. Additional causes of vitreous hemorrhage in younger patients include trauma, Valsalva retinopathy, Terson's syndrome, Eales disease, systemic clotting abnormalities, retinal cavernous or capillary hemangioma rupture, peripheral neovascularization from pars planitis, chronic uveitis, or talc retinopathy. Additionally, Fabry's disease was considered due to bilateral retinal arteriolar tortuosity.

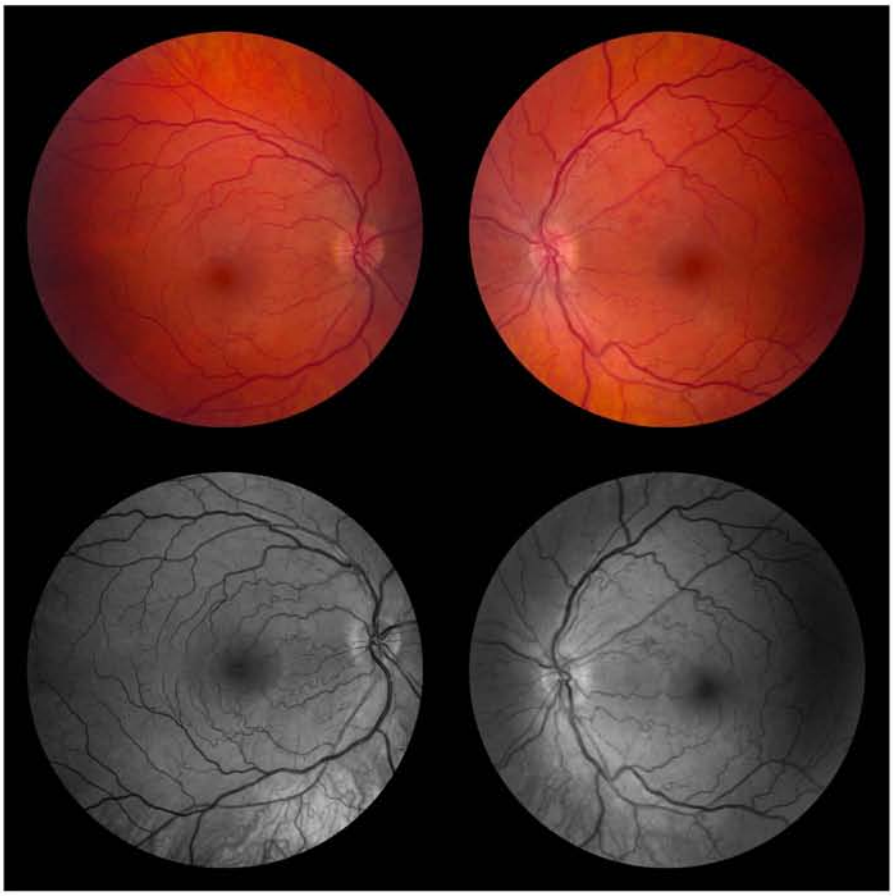


Figure 2

Given her already initiated medical workup, we discussed our findings with her internist and geneticist. A genetic workup was completed revealing a diagnosis of hereditary angiopathy with nephropathy, aneurysms, and muscle cramping syndrome.

Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps, or HANAC, syndrome is part of a group of conditions called the COL4A1-related disorders, affecting type IV collagen, on chromosome 13q14. HANAC syndrome is an exceedingly rare autosomal dominant condition with an unknown exact prevalence. Only six families have been reported in the literature.

HANAC syndrome is marked by multi-system angiopathy. Nephropathy with hematuria is common due to glomerular damage. Muscle cramps manifest early and can be spontaneous or triggered by mild exercise. Raynaud's phenomenon may be prominent due to abnormal nail bed capillaries. Patients with HANAC syndrome can also have neurologic involvement due to intracranial aneurysms with possible rupture causing hemorrhagic stroke.

Individuals with HANAC syndrome also have retinal arterial tortuosity and are prone to spontaneous

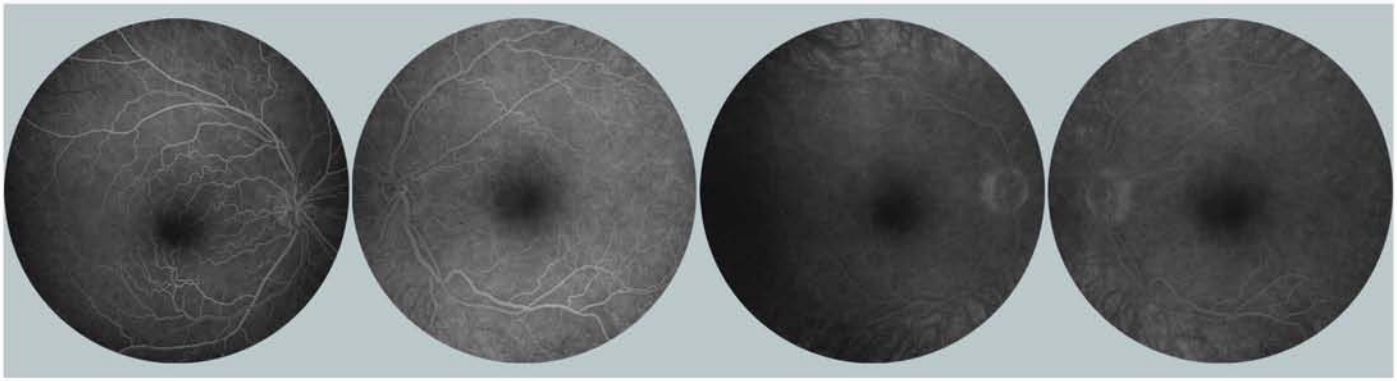
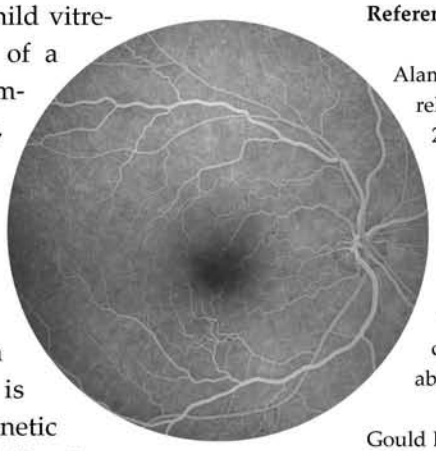
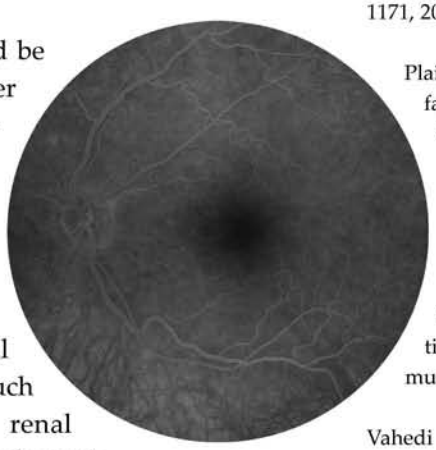


Figure 3

intraretinal hemorrhage and mild vitreous hemorrhage. One report of a family with three affected members described symptomatic, self-resolving vitreous hemorrhages after mild trauma in eyes with no leakage on fluorescein angiography. Although no known frequency exists, an association with Axenfeld-Reiger anomaly is present given the shared genetic association of COL4A1-related disorder.



Work-up and diagnosis should be performed in concert with other physicians and includes genetic testing. Hematologic analysis and urinalysis may be helpful. Skin biopsy can be supportive in demonstrating basement membrane abnormality at the dermoepidermal junction. Additional testing such as cerebral MRI/MRA and renal biopsy are guided by clinical judgment.



Our patient returned to the office with unchanged examination. Given her family's new diagnosis, all family members were advised to call with any new symptoms and will undergo periodic examination.

References:

Alamowitch S, Plaisier E, Favrole P et al. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. Neurology. 2009:1873-82.

Gekeler F, Shinoda K, Junger M et al. Familial retinal arterial tortuosity associated with tortuosity in nail bed capillaries. Arch. Ophthal. 2006:1492-1494.

Gould DB, Marchant JK, Savinova OV et al. Col4a1 mutation causes endoplasmic reticulum stress and genetically modifiable ocular dysgenesis. Hum. Molec. Genet. 2007: 798-807.

Gould DB, Phalan FC, Breedveld GJ et al. Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. Science 308: 1167-1171, 2005.

Plaisier E, Alamowitch S, Gribouval O et al. Autosomal-dominant familial hematuria with retinal arteriolar tortuosity and contractures: a novel syndrome. Kidney Int. 2005; 2354-2360.

Plaisier E, Chen Z, Gekeler F et al. Novel COL4A1 mutations associated with HANAC syndrome: a role for the triple helical CB3[IV] domain. Am J Med Genet A. 2010:2550-5.

Plaisier E, Gribouval O, Alamowitch S et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. New Eng. J. Med. 2007;2687-2695.

Vahedi K, Alamowitch S. Clinical spectrum of type IV collagen (COL4A1) mutations: a novel genetic multisystem disease. Curr Opin Neurol. 2011:63-8.

Van Agtmael T, Bailey MA, Schlotzer-Schrehardt UE. Col4a1 mutation in mice causes defects in vascular function and low blood pressure associated with reduced red blood cell volume. Hum. Molec. Genet. 2010; 1119-1128.