Familial CBL Gene Mutation Associated with Moyamoya disease and Retinal Degeneration: A Case Series

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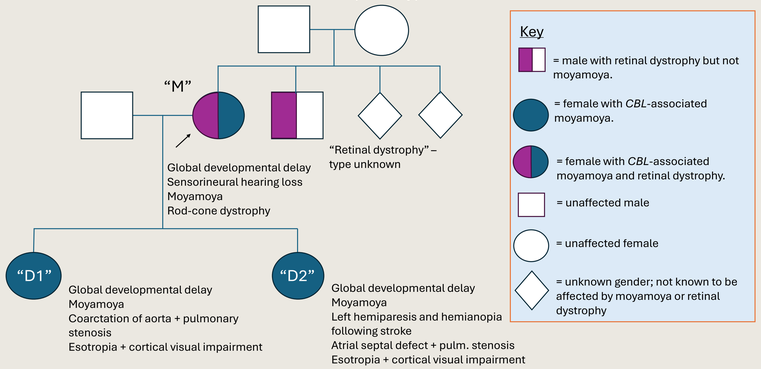
Background

- Certain mutations of the Casitas B-lineage Lymphoma (*CBL*) gene are known to cause a "RASopathy" syndrome. A recent case series by Fardeau et al[1] describes the ocular phenotype of this pathogenic variants of CBL, including features of rod-cone dystrophy and intraocular inflammation.
- *CBL* mutation is also reported as a rare cause of Moyamoya angiopathy, an inheritable vasculopathy characterised by carotid stenosis with downstream ischaemia and vascular remodelling/collateralisation which looks reminiscent of a "hazy puff of smoke" on angiography (Fig. 3), which is a rough translation of the term "moyamoya" in Japanese.
- We describe the first known reported case of a patient, "M", with coexistent rod-cone dystrophy and moyamoya disease, both thought to be caused by a pathogenic *CBL* mutation. We also briefly describe the ocular phenotype of her two female offspring (daughters 1 & 2; "D1"&"D2"), both of whom inherited this *CBL* variant and have features of moyamoya with coexistent ocular/visual pathology.

Figure 1: Family pedigree demonstrating autosomal dominant inheritance of *CBL*-mutation and associated phenotypes



Case Summary – "D1"

20m: Dx of global delay.
3y: Screening imaging triggered by her sister's diagnosis of moyamoya demonstrates features consistent with the same, as well as coarctation of the aorta and pulmonary stenosis.
7y: Multiple cranial burr holes.
5y: Cortical visual impairment.
10y: EUA ocular screen is normal with IOP 8mmHg BE.
11y: Care transferred to tertiary centre.

Case Summary – "D2"

4m: Right hemispheric cerebral infarction; angiography demonstrates collaterals consistent with moyamoya. Resulting left hemiparesis and global delay.
8m: Reduced VA noted with intermittent esotropia. Suspected left inattention. Fundoscopy normal. Occlusion commenced.
4y: Successful left EDAS revascularisation. Registered with sight impairment (VF loss + CVI).
10y: Suspected bilateral ocular ischaemic syndrome secondary to moyamoya; care transferred to tertiary centre where neovascular glaucoma confirmed on EUA, with drops & PRP.

Case presentation – "M"

- **Age 23:** Presents with headaches without red flags and 6/9 vision OU. Background of low hypermetropia, sensorineural hearing loss and mild global developmental delay in childhood. Ophthalmic review results in a diagnosis of pseudo-papilloedema with buried optic disc drusen and left pigmentary retinopathy. CT head is normal. Discharged.
- **Age 27:** Asymptomatic re-referral during 2nd trimester of 2nd pregnancy with marked bilateral disc swelling. VA 6/6 OD & 6/9 OS. Pigmentary retinopathy OU. Urinalysis and BP not suggestive of pre-eclampsia. MRI head normal.
  - Ophthalmic review 2/12 following delivery is stable.
  - Extensive right hemispheric infarct in her 4m-old daughter ("D2") with features of moyamoya on angiography. This prompts MRA in "M" and "D1" which demonstrates bilateral post-cavernous ICA occlusion after giving off ophthalmic arteries, with extensive posterior circulatory collaterals.
- **Age 31:** Genetic testing for the family failed to identify one of the eight mutations classically associated with moyamoya but instead revealed a shared heterozygous mutation in the *CBL*-gene.
- **Age 33-37:** Asymptomatic ophthalmic reviews reveal stable VA and normal IOP, bilateral PSC cataracts, peripheral pigmentary retinopathy (Figure 2), vascular attenuation, disc swelling and disc drusen on B-scan. There were no signs of intraocular inflammation. Formal perimetry revealed visual field constriction. Macular OCT was dry. Autofluorescence showed an irregular pattern of hypoAF and leading edge hyperAF (Figure 2). FFA revealed bilateral disc leakage, absent peripheral vasculature and no vasculitis or ischaemia. ICG was normal.
- **Age 37-38:** Successful left then right intracranial revascularisation procedures.
- **Age 38:** Progression of retinopathy with widefield colour photography and autofluorescence as below. Decision to not immunosuppress based on lack of evidence for benefit [1].

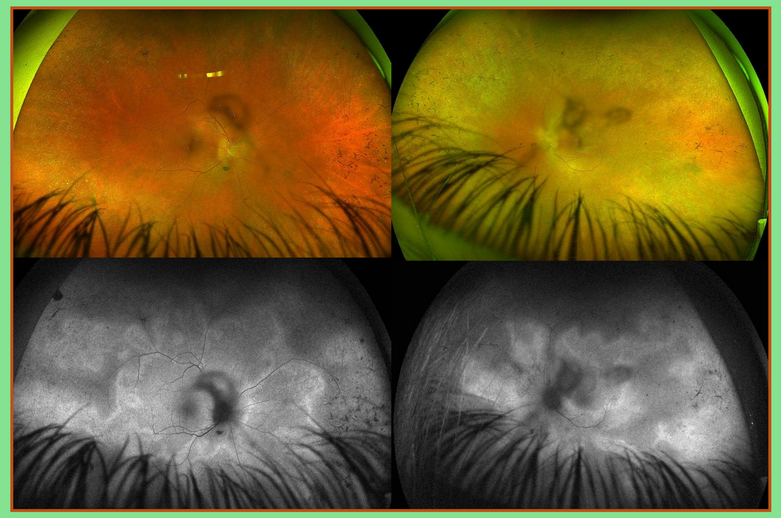


Figure 2: Widefield colour fundus photography demonstrating bone spicules, disc swelling and peripheral vascular attenuation. Autofluorescence demonstrating irregular patchy hypoAF with sharply demarcated leading edge hyperAF.

Discussion

- Whole exome sequencing identified a shared pathogenic *CBL* mutation on chromosome 11q, inherited in an autosomal dominant pattern from "M" to both daughters (Fig. 1). No pathogenic variants were found in the eight hereditary moyamoya (*MYMY*) loci (Fig. 4), described on "OMIM.org, and no retinal gene abnormalities were highlighted through whole exome sequencing, however testing focused primarily on known moyamoya and neurological genes.
- We hypothesise that the pathogenic *CBL* variant underlies the intracerebral vascular anomalies as well as the atypical rod-cone dystrophy in "M", as well as the cerebrovascular abnormalities in both daughters. In "D1" and "D2", secondary ischaemia from moyamoya likely contributed to ocular and visual pathology. Both developed cortical visual impairment, while "D2" additionally developed bilateral ocular ischaemic syndrome at age 10, complicated by uveitis and neovascular glaucoma following infantile right cerebral infarction.
- Retinal dystrophy is phenotypically heterogeneous and may mimic intraocular inflammation, with features such as cystoid macular oedema, vitritis, and optic disc leakage, yet these changes are often unresponsive to immunosuppression. "M"'s retinal findings were atypical for retinitis pigmentosa, with non-confluent peripheral hypo-autofluorescence and patchy preserved autofluorescence. Pathogenic CBL variants may promote aberrant signalling, protein accumulation, and secondary inflammatory effects. However, in a 2022 case series by Fardeau et al.[1], immunosuppression failed to improve ocular disease in five patients with pathogenic CBL mutations despite use of multiple agents; therefore, immunosuppression was not trialled in "M".

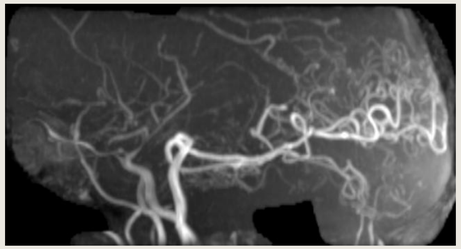


Figure 3: MR angiography after revascularisation, demonstrating chronic ICA occlusion and collateralisation

- **MYMY1:** 3p26-p24.2; AR inheritance.
- **MYMY2:** *RNF213* gene at 17q25.3; AR or AD inheritance.
- **MYMY3:** 8q23; inheritance unknown.
- **MYMY4:** Xq28l; XLR inheritance.
- **MYMY5:** *ACTA2* gene at 10q23.31; inheritance unknown.
- **MYMY6:** *GUCY1A1* gene at 4q32.1; AR inheritance.
- **MYMY7:** *ANO1* gene at 11q13.3; AR or AD inheritance.
- **MYMY8:** *NOS3* gene at 7q36.1; AR inheritance.

Figure 4: The eight gene loci for hereditary moyamoya described on www.OMIM.org

Conclusion

We present the case of a patient with **CBL mutation as the suspected cause for both moyamoya and an atypical rod-cone dystrophy**. Combined with the findings of Fardeau et al[1], this case highlights that **CBL mutations should be considered in moyamoya disease negative for MYMY1–7 loci, in R32-negative inherited retinal degeneration and in unexplained familial adult or complex paediatric uveitis**, including uveitic masquerade secondary to ocular ischaemia.

References:
[1] Fardeau C, Alafaleq M, Ferchaud MA, Hié M, Besnard C, Meynier S, Rieux-Laucat F, Roos-Weil D, Cohen F, Meunier I. *Casitas B-lineage lymphoma* Gene Mutation Ocular Phenotype. Int J Mol Sci. 2022 Jul 17;23(14):7868. doi: 10.3390/ijms23147868. PMID: 35887217; PMCID: PMC9318494.