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Case Report

Case Report: Asymmetric Retinal and Fundal Fluorescein Angiogram Findings in Col4A1 Mutation

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Abstract

Purpose: We aim to describe the fundal fluorescein angiography (FFA) findings in a patient with COL4A1 mutation which to date has not been described in this condition. We hope to highlight the variability in ocular phenotypes seen in COL4A1 mutation, even between eyes in the same patient. Methods: Case Report. Results: A 14 year-old girl with a history of cerebral palsy, cerebral visual impairment and COL4A1 mutation with porencephaly has been attending the eye service for bilateral aphakic glaucoma with previous bilateral glaucoma tube surgery on Latanoprost, Brinzolamide and Timolol to both eyes. She developed a spontaneous right vitreous haemorrhage and anterior chamber hyphaema, subsequently requiring a vitrectomy and anterior chamber washout due to elevated intraocular pressure. Intraoperatively, she was noted to have extensive ischemic changes in the right eye. In her left fundus, there were sclerosed arterioles emanating from the disc, with the rest of the retina being normal. Despite the vitrectomy, the right eye vitreous haemorrhage and hyphaema recollected over time with persistently high intraocular pressure. She underwent a repeat vitrectomy and washout, subsequent cyclodiode laser and evisceration after she developed a painful blind right eye. During the course of her treatment, a FFA for her left eye was performed. Delay in arm-retinal time and a “fern-leaf” pattern of capillary leakage was noted. Discussion: The disease resulting from COL4A1 mutation is extremely variable. We report a patient with COL4A1 mutation with asymmetric retinal pathology with one eye eventually needing evisceration. This case highlights the need to have a high index of suspicion for early detection and asymmetric disease. There should be a low threshold for further evaluation such as FFA or optical coherence tomography (OCT) angiography to evaluate for ocular perfusion. Although COL4A1 is a systemic disease, it can have asymmetric presentation between two eyes.

Keywords

Angiogram, Col4A1, Heterogenous, Retina

1. Introduction

The COL4A1 gene on chromosome 13q34 encodes the alpha 1 chain of type IV collagen, which is a component of basal membranes expressed mainly in the brain, muscles, kidneys and eyes [1]. Mutations in COL4A1 can cause multisystem disorders with extremely variable human phenotypes, with disease onset as early as in the fetal period. Neurological manifestations such as cerebral microangiopathy, familial poren-

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cephaly [1, 2]https://jamanetwork.com/journals/jamaophthalmology/fullarticle/425446 - ref-eog90011-1, neonatal and adult intracerebral haemorrhages, small vessel disease of the brain and aneurysms have been reported. In the eye, associated findings include keratoconus, cataract, posterior lenticonus, anterior segment dysgenesis, retinal arteriolar tortuosity and retinal haemorrhages [3-5]. There is in addition a specific phenotype called HANAC (hereditary angiopathy with nephropathy, aneurysm, and muscle cramps) [5-7].

Few studies have provided detailed retinal imaging and findings in association with COL4A1. In our study, we aim to describe the FFA findings in a patient with COL4A1 mutation which to date has not been described previously in this condition. We also hope to highlight the variability in ocular phenotypes seen in COL4A1 mutation, even between eyes in the same patient.

2. Case Report

A 14 year old girl with a history of cerebral palsy, cerebral visual impairment and COL4A1 mutation with porencephaly has been attending the eye service for bilateral aphakic glaucoma with previous bilateral glaucoma tube surgery on Latanoprost, Brinzolamide and Timolol to both eyes. She had no significant family history of note. She developed a spontaneous right vitreous haemorrhage and anterior chamber hyphaema. B-mode ultrasound did not demonstrate any retinal breaks or detachment on serial monitoring. The vitreous haemorrhage and hyphaema were non-resolving but as she was relatively comfortable with normal intraocular pressures (IOP), the family's preference was to observe. Her right IOP subsequently elevated to 30mmHg and she was listed for an urgent vitrectomy and anterior chamber washout. Intraoperatively, she was noted to have extensive right rubeosis iridis with right retinal ischemia and vitreous membranes, widespread vascular occlusion, new vessels at the optic disc and macular subhyaloid haemorrhage. In the left fundus, there were sclerosed arterioles emanating from the disc (Figure 1). The retinal venules were otherwise grossly normal with no retinopathy or ectatic vessels noted. There were no new vessels or signs of ischaemia. Despite the vitrectomy, the right eye vitreous haemorrhage and hyphaema recollected over time with persistently high intraocular pressures. A repeat right eye anterior chamber washout and vitrectomy was scheduled, along with a FFA for her left eye in view of the vascular anomalies noted in the fellow eye previously. Intraoperatively, she was found to have a funnel shaped detachment in her right eye which was assessed to be inoperable. Cyclodiode laser was thus performed to control IOP for her right eye. FFA performed for her left eye. (Figure 2) revealed delay in arm-retinal time with the arteriovenous phase at 34 seconds, with persistent patchy and mottled choroidal filling. Figures 3, 4 show twig-like abnormalities of retinal vasculature with no significant areas of peripheral ischemia or capillary fallout. A "fern-leaf" pattern of capillary leakage and pinpoint areas of hyperfluoresence were visible in the temporal and inferotemporal quadrant (Figure 3). This persisted into the later phases of the FFA (Figure 5). Her IOP in the right eye remained elevated and developed in a painful blind eye. She subsequently underwent right eye evisceration. The left eye has not to date developed any retinal neovascularisation or rubeosis, after two years' follow-up but ongoing treatment for the pre-existing aphakic glaucoma has been required.

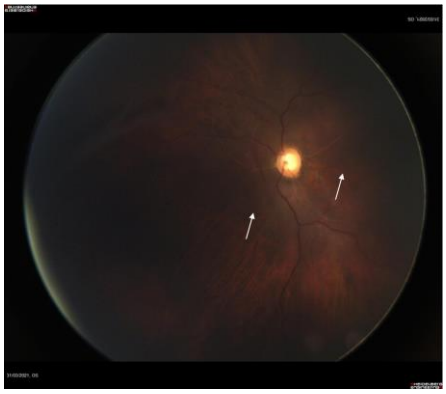

Figure 1. *Left eye fundal photo: Sclerosed ghost-like arterioles emanating from the disc (labelled with arrow). Retinal venules were otherwise grossly normal with no retinopathy or ectatic vessels noted.*

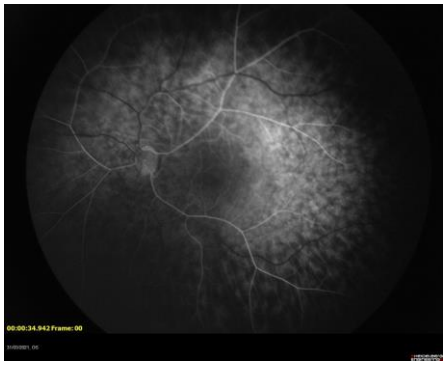

Figure 2. *Left eye FFA: Delay in arm-retinal time with the arteriovenous phase at 34 seconds, with persistent patchy and mottled choroidal filling.*

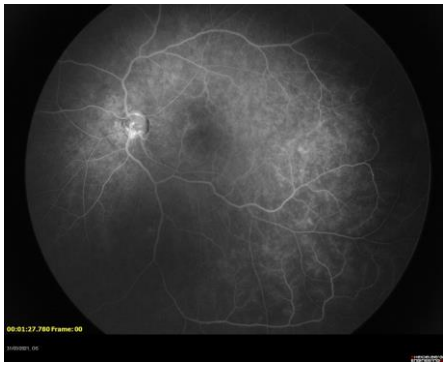

Figure 3. *Left eye FFA: "Fern-leaf" pattern of capillary leakage and*

pinpoint areas of hyperfluoresence is visible in the temporal and inferotemporal quadrant.

Figure 4. *Left eye FFA: Twig-like abnormalities of retinal vasculature with no significant areas of peripheral ischemia or capillary fallout.*

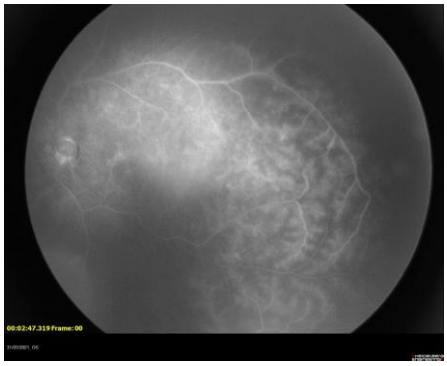

Figure 5. *Left eye FFA: Late phase.*

3. Discussion

The COL4A1 gene is located on the 13q34 chromosome and contains 52 exons, which encodes the α1 chain of collagen IV. Members of the type IV collagen family are essential components of all basement membranes and define structural stability as well as tissue-specific functions [1]. The clinical spectrum of COL4A1 mutations has progressively enlarged, with evidence of neonatal and adult intracerebral hemorrhages, aneurysms, ocular manifestations of variable type, and nephropathy [1-5]. Most COL4A1 mutations are autosomal dominantly inherited, but the phenotypic spectrum is highly heterogeneous. The disease resulting from COL4A1 mutation is extremely variable [8]. Additional modifying factors, either environmental or genetics, are likely involved and remain to be identified. Sporadic individuals with severe presentation may harbor a de novo mutation [8].

Allelic heterogeneity may contribute to the phenotypic heterogeneity observed. Mutations involving glycine residues that belong to exons 24-25 of COL4A1 are involved in the HANAC syndrome. These mutations cluster in a CB3 (IV) region of the triple-helical domain, which encompasses major integrin-binding sites [9]. Genotype-phenotype correlation studies conducted in patients mutated in a triple-helix glycine residue suggest a position-dependent effect of the mutation on the phenotype. Substitutions involving a glycine located in the C-terminal part the triple-helix tend to be associated with brain haemorrhage that occur at a younger age and are more severe that those located in the N-terminal part [10]. The presence of retinal artery hypertortuosity is highly penetrant in Glycine substitutions involving the first N-terminal third of the helix domain, as compared to substitutions near to the C-terminus that are more prone to the development of eye congenital malformations [10]. Mice experiments also suggest that the biological impact of quantitative mutations is milder than dominant negative mutations. However, genotype-phenotype correlation analyses conducted in patients failed to demonstrate that quantitative mutations are associated with a milder phenotype [10]. These observations still need to be replicated and refined by additional studies. While it is known that heterogeneity occur between patients, our report highlights the asymmetric presentation that can happen between two eyes, even in the same patient.

Our patient developed strikingly asymmetrical retinal pathology – the right eye developed neovascular glaucoma with widespread retinal ischemia, neovascularisation and eventual tractional retinal detachment. It subsequently required evisceration for a painful blind eye. The fundus on the left eye, on the contrary, had no significant ischemia or retinal tortuosity, as confirmed on intra-operative FFA, despite the significantly attenuated retinal arterioles. This case highlights the need to have a high index of suspicion for asymmetric disease and a low threshold for further evaluation such as FFA or OCT angiography to evaluate for ocular perfusion. Although COL4A1 is a systemic disease, it can have asymmetric presentation between two eyes. This case also highlights the importance of early detection and high index of suspicion for retinal ischemia, with FFA a useful investigation in these patients.

Few studies have provided detailed retinal imaging and findings in association with COL4A1. A study by Zenteno et al published retinal findings associated with familial retinal arteriolar tortuosity (FRAT) in cases with COL4A1 mutations [11]. Alavi et al investigated retinal pathology in mice carrying dominant-negative COL4A1 mutations by examining retinas longitudinally in vivo using FFA, fundoscopy and OCT. Retinal examinations revealed serous chorioretinopathy, retinal hemorrhages, fibrosis or signs of pathogenic angiogenesis with chorioretinal anastomosis in up to approximately 90% of COL4A1 mutant eyes depending on age and the specific mutation [12]. These findings were not seen in our patient.

4. Conclusion

In conclusion, we report a patient with COL4A1 mutation with asymmetric retinal pathology with one eye eventually needing evisceration. Few studies have provided detailed retinal imaging and findings in association with COL4A1. There

can be wide variability of ocular phenotypes related to COL4A1, even between eyes in the same patient. There should be a high index of suspicion for early detection with early consideration of FFA or OCT angiography to evaluate for ocular perfusion.

Abbreviations

FFA	Fundal Fluorescein Angiography
OCT	Optical Coherence Tomography
HANAC	Hereditary Angiopathy with Nephropathy, Aneurysm, and Muscle Cramps
IOP	Intraocular Pressure
FRAT	Familial Retinal Arteriolar Tortuosity

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Author Contributions

Yan Tong Koh: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing

Conrad Schmoll: Supervision

Conflicts of Interest

The authors declare no conflicts of interest.

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