Case report

Advanced coats-like retinopathy as the initial presentation of Familial Retinal Arterial Macroaneurysms

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ABSTRACT

Purpose: To describe two young Saudi brothers with bilateral progressive retinal arterial aneurysms and a subtotal exudative retinal detachment with Coats-like presentation in the older sibling as the initial presentation of Familial Retinal Arterial Macroaneurysms (FRAM).

Observations: Two young Saudi brothers with a family history of consanguinity presented with the classic clinical presentation and genetic identification of FRAM. In this report, we describe the presence of prominent peripheral retinal capillary changes mimicking Coats’ disease.

Conclusions and importance: FRAM can present similar to bilateral Coats’ disease and should be considered in the differential diagnosis of Coats-like retinopathy. The diagnosis of FRAM may have a significant implication because of the associated cardiac abnormality, such as supravalvular pulmonary stenosis, which should be evaluated by echocardiography and managed accordingly.

1. Introduction

Familial Retinal Arterial Macroaneurysms (FRAM), first described and named in 2002 by Dhinsa and Abboud, is a rare autosomal recessive disease characterized by retinal arterial beading, aneurysm formation along the major arterial trunks, hemorrhage and exudation. Some patients manifest Coats-like vascular changes with peripheral capillary dropout, telangiectasia and aneurysmal dilatation. A founder mutation in insulin-like growth factor binding protein 7 (IGFBP7) has been identified in 22 patients from eight Saudi families. Supravalvular pulmonary stenosis, an important extraocular finding, was present in all 13 patients who were evaluated by echocardiography. Coats’ disease is an idiopathic condition characterized by telangiectatic vessels, capillary non-perfusion, aneurysmal dilatations, and exudation. It affects boys more commonly and usually presents unilaterally. Bilateral involvement occurs in 5% of cases and usually raises the suspicion of a systemic disease associated with Coats’-like retinopathy. Herein we describe two young Saudi brothers with a family history of consanguinity who presented with bilateral progressive retinal arterial aneurysms and a subtotal exudative retinal detachment with Coats-like presentation in the older sibling as the initial presentation of FRAM.

2. Findings

2.1. Case 1

A 7-year old boy initially presented at the age of 5 years when he was noted to have intermittent exotropia in his left eye and was brought in for evaluation. His medical history was significant for an echocardiographic diagnosis of mild supravalvular pulmonary stenosis prompted by a cardiac murmur on routine examination. Best corrected visual acuity (BCVA) was 20/100 in the right eye and 3/200 in the left eye. The intraocular pressure (IOP) was normal in both eyes. Anterior segment examination was unremarkable in both eyes. Ophthalmoscopy of the right eye revealed subretinal hard exudates at the superotemporal arcade with minimal foveal involvement. Clinically visible
aneurysms were noted in the midperiphery. Ophthalmoscopy of the left eye revealed subtotal exudative retinal detachment along with obvious vascular telangiectasia superotemporally (Fig. 1A and B). Fluorescein angiography (FA) highlighted a subtle major arterial trunk beading, mid-peripheral and peripheral aneurysms and capillary dropout in all four quadrants in the right eye (Fig. 1C) and peripheral aneurysms and non-perfusion in the left eye (Fig. 1D). The constellation of findings suggested the diagnosis of FRAM. Genetic testing identified the presence of a homozygous splicing mutation in IGFBP7 intron 4 which confirmed the diagnosis. The patient underwent indirect argon laser photocoagulation, with power ranging from 150 to 200 mW and duration between 200 and 400 milliseconds, applied over the peripheral aneurysms, the inferotemporal aneurysm in the near periphery of the right eye and the visible peripheral aneurysms in the left eye. Due to suboptimal outcome, the left eye was injected with intravitreal triamcinolone acetonide 2 mg/0.05 ml. Follow up at 3 weeks showed partial reduction of subretinal fluid (SRF) in the left eye but not enough to allow further laser treatment. Subsequently, the left eye underwent external drainage of SRF, cryotherapy and indirect laser photocoagulation. The retina was reattached in the left eye and anatomic stabilization was achieved in both eyes (Fig. 1E and F). At 2-year follow up, BCVA improved to 20/50 in the right eye and to 20/400 in the left eye. The cardiac condition was mild and only required annual assessment.

Family pedigree and DNA sequence results of the IGFBP7 gene (Fig. 2) identified two affected siblings (Case 1 & 2) and the father was heterozygous for the mutation (carrier) and had a normal fundus. The mother and five siblings, aged 4–24 years, have not been tested or examined, but remained asymptomatic.

2.2. Case 2

A 2-year old boy was evaluated as a part of family screening for FRAM. A general medical examination by a pediatric cardiologist revealed a mild supravalvular pulmonary stenosis with pressure gradient of 30 mmHg with normal cardiac function and chamber size that needed no further intervention and only required annual assessments. The child was fixing and following light in both eyes. IOP was normal in both eyes. Anterior segment examination was unremarkable in both eyes. Ophthalmoscopy of the right eye revealed subfoveal gliotic tissue with superior macular subretinal hard exudates associated with prominent beading of the all first-order branches of the arterial trunk with macroaneurysms formation, more prominent in the right (Fig. 3A) than the left eye. The periphery showed capillary dropout, prominent...
fig. 3b and c). Genetic testing, identified the presence of a homozygous splicing mutation in IGFBP7 intron 4 which confirmed the diagnosis. The patient underwent indirect argon laser photocoagulation in both eyes with similar settings as the first patient. At 2-week follow up, examination revealed marked leakage with extensive submacular exudates from all the major arterial trunks with mild exudative macular thickening of the right eye. The patient underwent intravitreal injection of triamcinolone acetonide 2 mg/0.05 ml in the right eye with more indirect laser to the leaking aneurysm guided by the FA under sedation. Follow up at 2-week intervals with further laser treatment twice for right eye and once for left eye lead to complete regression of the SRF and partial regression of the subretinal exudates with secondary subretinal gliosis and epiretinal membrane formation (Fig. 3D). Anatomic and functional stabilization was achieved in both eyes at 4-month follow up.

3. Discussion

The hallmark of FRAM is the presence of retinal arterial beading in the major trunks and macroneurysm formation. The aneurysms were noted to arise from areas with beading and have the tendency to bleed into the vitreous cavity, sub-hyaloid/sub-internal limiting membrane spaces and subretinal space. Leaking aneurysms result in intraretinal and subretinal exudates and if severe enough, exudative retinal detachment. Consequently, pigmentary changes and subretinal gliosis may occur secondary to the subretinal process. Despite the presence of vascular sheathing in some cases, no signs of active inflammation were noted. Interestingly, only one patient manifested Coats-like changes at the capillary bed level. A subsequent study of 22 subjects highlighted two additional features of the disease: the autosomal-recessive inheritance pattern, and its association with supravalvular pulmonary stenosis. Furthermore, the clinical spectrum of the disease was expanded and noted that beading may extend into the retinal periphery.

In case 1, marked Coats-like changes were noted in both eyes, more pronounced in the left eye. In addition, the major arterial trunk beading was so subtle to the degree that it can be easily missed. Bilateral Coats’ disease is extremely rare and a search for a systemic association may be warranted. The most common systemic association is facioscapulohumeral dystrophy (FSHD), an autosomal dominant disease characterized by a muscle weakness involving the face, shoulders, descending to the abdomen and lower limbs in advanced stages. Extravascular manifestations include hearing loss in 50% and Coats-like changes in 75% of cases. Cardiac abnormalities have been reported in FSHD and include conduction defects and hypertrophic cardiomyopathy. The first patient did not show features of muscle weakness which usually precede the ocular findings. However, Shields et al. reported a 2-year old girl with advanced Coats-like telangiectasia and neovascular glaucoma who later on developed muscle weakness suggestive of FSHD. Given all the findings in the first patient, and the subtle beading, FSHD was investigated as a possible diagnosis. Systemic evaluation was normal apart from the supravalvular pulmonary stenosis. Genetic testing was negative for FSHD as well.

In FRAM, a founder splicing mutation in IGFBP7 has been identified, which leads to defective protein. IGFBP7 is expressed in the vasculature smooth muscles; that affects larger branches of the retinal arterial vasculature where the pressure is highest and the mechanical integrity of the artery is reduced; but not in smaller capillaries which explains the retinal phenotype. However, Coats-like changes at the capillary level are not explained by the primary mutation, and may be in part, a secondary phenomenon. Peripheral retinal findings were quite prominent in both patients and may be a secondary phenomenon related to the disease severity.

The management of FRAM depends on the clinical presentation and involves laser photocoagulation to the leaking macroaneurysms, vitrectomy for non-resolving hemorrhage, submacular blood displacement and external drainage in exudative detachment as in case 1. We elected to use intravitreal triamcinolone as an intermediary step because of the previous experience with triamcinolone use in Coats’ disease. Triamcinolone may help in resorption of the SRF to allow photocoagulation and avoid the need for incisional surgery. However, this had a very limited effect in both patients in the current report. The clinical course appears to be unpredictable with periods of quiescence and reactivation.

4. Conclusions

Familial Retinal Arterial Macroneurysms is a rare progressive autosomal recessive disease that represents a unique opportunity to observe the consequences of germline mutations on vasculogenesis and angiogenesis. FRAM can present with prominent peripheral capillary changes similar to bilateral Coats’ disease and should be included in the differential diagnosis of Coats-like retinopathy. Genetic testing and cardiac evaluation are important to distinguish FRAM from Coats’ disease. Supravalvular pulmonary stenosis, a known association with FRAM, should be evaluated by echocardiography and managed according to its severity.
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 any patient.

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Conflicts of interest

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Authorship

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2018.04.007.
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