American Journal of Ophthalmology Case Reports 19 (2020) 100715

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc

Case report

Adams Oliver syndrome: A mimicker of familial exudative vitreoretinopathy

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ARTICLE INFO

Keywords:
Adams oliver syndrome
Aplasia cutis
Familial exudative vitreoretinopathy
Tractional retinal detachment

ABSTRACT

Purpose: To describe an infant with Adams Oliver syndrome (AOS) with ocular signs similar to familial exudative vitreoretinopathy.

Observations: A full-term female infant presented with a congenital scalp defect, hypoplasia of the fingers and toes along with a radial retinal fold in the right eye and tractional retinal detachment in the left eye. Fluorescein angiography findings included peripheral retinal nonperfusion, irregular vascular sprouting beyond the vascular-avascular junction, pinpoint areas of hyperfluorescence as well as late peripheral and posterior vascular leakage. The patient was clinically diagnosed with Adams Oliver syndrome based on the collective findings. Laser photocoagulation to the avascular retina was performed in both eyes which resulted in stabilization of the condition after 2 years of follow up.

Conclusion and importance: The ocular phenotype in AOS may be similar to familial exudative vitreoretinopathy. Therefore, suspicion of the diagnosis should prompt ophthalmic evaluation including fluorescein angiography to detect and possibly treat the ischemic retinopathy.

1. Introduction

Adams-Oliver syndrome (AOS), first described in 1945, is a rare inherited condition characterized by a combination of congenital scalp defect (aplasia cutis congenita) and variable degree of transverse limb defects.[1] Most cases are autosomal dominant (mutation in *DLL4, ARHGAP31, RBPJ,* and *NOTCH1*) with variable penetrance. However, some cases were reported as autosomal recessive (mutation in *EOGT* and *DOCK6*).[2–7] It is hypothesized that the underlying pathogenesis of AOS is a congenital vasculopathy, which may involve the cardiovascular system, brain, liver, lungs, eyes, and skin.[8] It is frequently associated with Cutis marmorata telangiectatica congenita, a skin condition characterized by marbeled blue or purple skin discoloration due to cutaneous vascular anomaly.[9,10] There have been few reported cases of AOS associated with retinal findings,[11–14] and one case with congenital cataract.[15] We report a case of a young female with AOS associated with retinal findings and psychomotor retardation.

2. Case report

A seven-week-old girl was referred to King Khaled Eye Specialist Hospital (KKESH) for suspicion of bilateral retinal detachments. The child was a product of full term normal spontaneous vaginal delivery. Prenatal history was unremarkable. The parents are first-degree relatives. The parents and her three male siblings have not had ophthalmic examination but are healthy otherwise. On extended family history, a 16-year-old female cousin from the father's side was reported to have short stature, mental retardation, short fingers with abnormal nails and poor vision but she was not available for examination.

The proband's birth weight was within the normal range. At birth, swelling and redness of the scalp was noted which was considered as a skin infection and managed accordingly by the referring hospital. At presentation to KKESH, the patient exhibited a light aversion response bilaterally but with poor fixation. Examination under sedation revealed normal intraocular pressure in both eyes. Anterior segment examination of both eyes was unremarkable apart from posterior embryotoxon. Fundoscopic examination of the right eye revealed a dry radial falciform retinal fold extending from the macula to temporal periphery. There was an abrupt termination of vascularization temporally at the equator and straightening of vessels, but no neovascularization or exudation were noted. Fundoscopic examination of the left eye showed temporal tractional retinal detachment involving the macula with preretinal fibrous proliferation and hemorrhage.

Examination under anesthesia after six weeks revealed unchanged status of the right eye and resolution of the preretinal blood in the left eye with persistent tractional retinal detachment due to temporal

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https://doi.org/10.1016/j.ajoc.2020.100715
Received 1 March 2019; Received in revised form 2 April 2020; Accepted 13 April 2020
Available online 22 April 2020

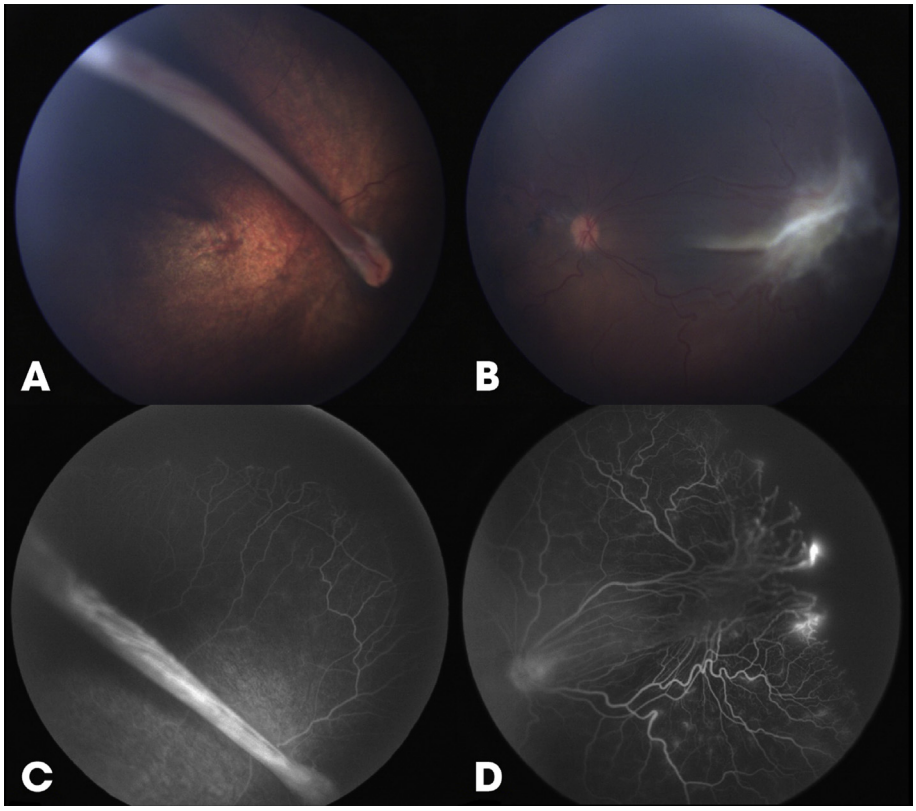

Fig. 1. (A) Fundus photograph of the right eye showing a dry radial retinal fold. (B) Fundus photograph of the left eye showing a temporal proliferation causing tractional retinal detachment involving the macula. (C and D) Fluorescein angiogram of both eyes depicting peripheral nonperfusion.

epiretinal fibrous proliferation (Fig. 1A and B). Fluorescein angiography (FA) findings in both eyes included peripheral retinal nonperfusion, irregular vascular sprouting beyond the vascular-avascular junction, pinpoint areas of hyperfluorescence as well as late peripheral and posterior vascular leakage. Laser photocoagulation was performed to ablate areas of ischemia avoiding the elevated parts of the retina. We recommended pars plana vitrectomy and membrane delamination of the left eye, however, the parents declined surgery.

Systemic examination was significant for scarring of the scalp vertex (Fig. 2A), hypoplasia of the digits of the left hand and foot along with absent or dystrophic nails (Fig. 2B and C), and gross psychomotor retardation. Brain computed tomography scan showed periventricular calcifications along with dilated lateral ventricles. Bone defects at both parietal parasagittal bones were noted. Echocardiography performed soon after birth revealed the presence of a small atrial septal defect and a moderate patent ductus arteriosus. Based on these collective clinical findings, the diagnosis of Adams-Oliver syndrome with familial exudative vitreoretinopathy (FEVR)-like picture was suspected. Genetic testing was not performed due to institutional limitations to access to genetic testing.

The patient was monitored regularly every 6 months. At 2-year follow up, the right eye remained unchanged but the left eye showed resolution of the submacular fluid, macular dragging with a notable dry macular fold and retinal pigment epithelial changes as a result of chronic submacular fluid.

3. Discussion

We described a patient with AOS presenting with an ocular phenotype similar to familial exudative vitreoretinopathy (FEVR). The frequency of ocular involvement in AOS is not known but to the best of our knowledge, there have been few reports of AOS describing associated retinal findings. The first report described two siblings with bilateral findings of mild microphthalmia and retinal detachment with a fold in the older sister and a unilateral falciform retinal fold in the younger brother. The fellow eye was declared normal although no FA was performed.[10] The second report was about a male infant who presented at birth with features of AOS associated with bilateral radial retinal folds involving the macula.[11] Another report in 2012 described a two-week-old girl who manifested with prominent iris vessels, posterior retinal arterial narrowing and venous dilatation, peripheral avascular retina with capillary dropout, arteriovenous anastomosis and telangiectasia in the right eye. The left eye was microphthalmic with microcornea, corneal leukoma, and temporosuperior scleralization.[12] A more recent report described two patients with AOS, one with avascular retinal periphery on FA but with leakage, and the second one manifested bilateral extensive fibrovascular proliferation with retinal detachment.[14] Our patient had somewhat similar ocular findings to previously reported patients, which suggest a pattern of ocular presentation among patients with AOS. We believe that all patients with suspected AOS should undergo early ocular examination and FA to rule out ocular involvement.

There are few diseases that have FEVR-like ocular phenotype associated with cutaneous abnormalities. These include incontinentia pigmenti,[16] dyskeratosis congenita[17] and cutis marmorata telangiectatica congenita.[18] The latter could be associated with AOS. Apart from the scalp and digit abnormalities, our patient did not have other skin changes. On the other hand, aplasia cutis associated with ocular abnormalities could be seen in Knobloch syndrome which typically presents with high myopia and rhegmatogenous retinal detachment rather than tractional retinal detachment.[19]

Most retinal folds in mature infants are likely associated with FEVR and wide-field FA is necessary to detect the avascular retinal periphery. Laser ablation of the avascular retina reduces future complications such as progressive retinal traction, rhegmatogenous retinal detachment and retinal exudation.[20] The approach to the retinal fold depends on

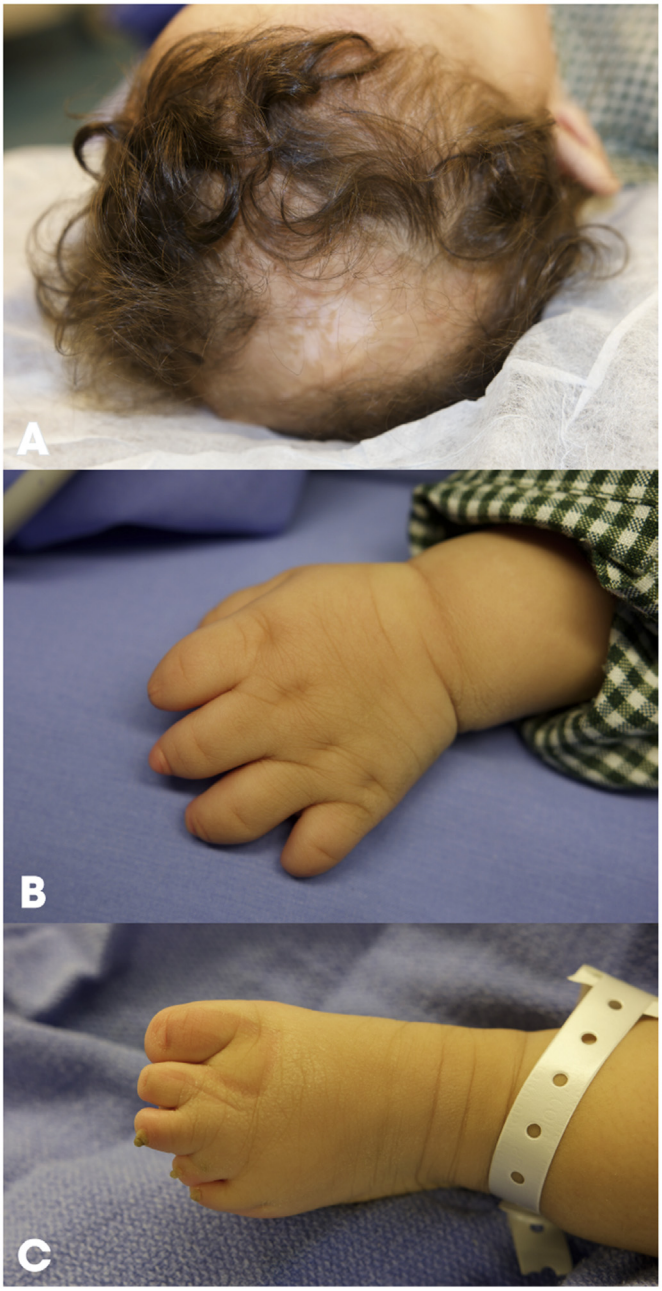

Fig. 2. (A) Photograph of the scalp showing scarring, depigmentation and loss of hair in the vertex area. (B and C) Photographs of the left hand and foot demonstrating hypoplasia of the fingers and toes along with absent or dystrophic nails.

whether the retinal fold is dry (photoreceptor to photoreceptor apposition) or wet (associated with subretinal fluid or exudation). The right eye in our patient had a dry retinal fold and surgical intervention will have a very little gain if any. The left eye however, had subretinal fluid at presentation and vitrectomy with membrane delamination could have resulted in retinal reattachment.

All cases of AOS with retinal findings had poor prognosis with either early death or developmental delay and blindness. The lack of internal organ involvement carries a better prognosis and normal life expectancy.[10] The presentation of AOS varies widely. Central nervous system involvement includes corpus callosum hypoplasia and periventricular calcification with some degree of psychomotor retardation.[11–13,21] Cardiac involvement includes ventricular septal defect, atrial septal defect, tetralogy of fallout, coarctation of the aorta, pulmonary venous stenosis and pulmonary hypertension.[8,11,22,23] Hepatoportal sclerosis was also reported in some patients.[8,17]

Familial exudative vitreoretinopathy is a Wnt signaling pathway disease characterized by incomplete retinal vascularization. Wnt signaling plays a major role in retinal vascular development and mutations in several genes involved in this pathway lead to the clinical phenotype.[24] FEVR is typically not associated with extraocular features except in *LRP5* mutations, which cause osteoporosis pseudoglioma.[25] On the other hand, AOS with mutations in *DLL4, RBPJ,* or *NOTCH1* involves the Notch signaling pathway which plays a crucial role in developing blood vessel walls.[6] Abnormal pericyte recruitment appears to be the basic pathogenic process in altered Notch pathway-mediated AOS. In an autopsy study, blood vessels demonstrated intimal damage along with vascular stenosis or dilatation, based on exuberant or poor vascular smooth muscle coverage with pericytes.[26] A study on mice revealed that blocking of Notch signaling pathway at late gestational age resulted in abnormal vasculogenesis and hemorrhage at the scalp and terminal limb of the developing embryo.[27] The pathogenesis of AOS with mutations in *DOCK6* or *ARHGAP31* is more complex and involves dysfunctional Cdc42/Rac1signaling which is critical in angiogenesis.[28,29]

Due to the genetic heterogeneity and variable penetrance of AOS, genetic testing is essential to help in confirming the diagnosis, genetic counselling and ruling out the presence of concurrent FEVR genes mutations. We recommend family members examination and ultra-wide field FA in suspected cases.

4. Conclusion

The ocular phenotype in Adams Oliver syndrome may be similar to familial exudative vitreoretinopathy. Therefore, suspicion of the diagnosis should prompt ophthalmic evaluation including fluorescein angiography to detect and possibly treat the ischemic retinopathy.

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 the patient.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

All authors have no financial disclosures.

Acknowledgement

None.

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