Case Report

Novel Genetic Inheritance with a Rare Presentation of Adams–Oliver Syndrome

Abdullah Abualait, Salaheldin Alfadni, Hala Edris, Mohammed Alshahrani, Mohamed Hanifa, Tariq Aziz, Wifag Alobeid, Ayed Al-Mordy

Department of Dermatology, King Fahad Armed Forces Hospital, Khamis Mushayt, Saudi Arabia

Abstract

Adams–Oliver syndrome (AOS) is a rare heterogeneous inherited disorder, characterized by the combination of the congenital scalp and terminal transverse limb defects. Various expressions of AOS have been reported. Most cases of the syndrome appear to follow autosomal dominant inheritance, but autosomal recessive inheritance has also been reported. However, genetic inheritance involving both autosomal recessive and dominant genes within the same patient was not previously reported. We report a newborn case of AOS with novel genetic profile and a rare clinical presentation.

Keywords: Adams–Oliver syndrome, aplasia cutis congenita, brachydactyly

Introduction

Adams–Oliver syndrome (AOS) is a rare developmental disorder with cutaneous, skeletal, cardiovascular, and neurological manifestations. Aplasia cutis congenita of the scalp vertex is the most common skin manifestation, and reported skeletal features of the syndrome are the terminal transverse limb defects manifested as amputations, syndactyly, brachydactyly, or oligodactyly.[1] Cutis marmorata telangiectatica congenita, pulmonary hypertension, portal hypertension, and retinal hypovascularization are frequently observed vascular anomalies. In some cases, neurological problems as well as cardiovascular defects have been described which were attributed to mutations in NOTCH1.[2] Adams and Oliver were the pioneers to describe the syndrome as an autosomal dominant disorder. Nevertheless, sporadic occurrence has been described.[3] Six genes have been linked to AOS; mutation of any of them can cause the syndrome. However, in some cases, the genetic cause is unknown.[4]

Case Report

A 2-day-old female infant admitted to the neonatal intensive care unit at King Fahad Armed Forces Hospital southern region, Saudi Arabia, for scalp lesions and limb deformities. She is the fourth child for her parents who are first-degree relatives. She was a full-term baby, born through a normal vaginal delivery with a birth weight of 2.6 kg. Her mother had hypothyroidism treated with oral thyroxine 25 mg/daily. She had seven previous pregnancies; the first four were the first-trimester abortions with an unidentified cause, and the next three were normal.

On examination, two scalp defects (cutis aplasia) were identified [Figure 1]. All fingers and toes showed brachydactyly [Figure 2]. Localized cutis marmorata on the lower part of the abdomen [Figure 3] was observed. Eye abnormalities identified on ophthalmologic examination included bilateral corneal detachment and chorioretinitis, defects that resulted in blindness. The echocardiogram displayed patent ductus arteriosus, and head computed tomography showed bone defect at both parietal and parasagittal bones [Figure 4]. Complete blood counts and liver and renal function tests were normal. Her scalp ulcers healed with scarring following 3-week treatment with local dressing and topical 2% fusidic acid cream.

Genetic study was done in Bioscientia Institute for Medical Diagnostics, Germany. The baby is a unique case of

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Address for correspondence: Dr. Abdullah Abualait, Department of Dermatology, King Fahad Armed Forces Hospital, Khamis Mushayt, Saudi Arabia.
E-mail: sabualiat@gmail.com

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Figure 1: Two scalp (vertex) defects

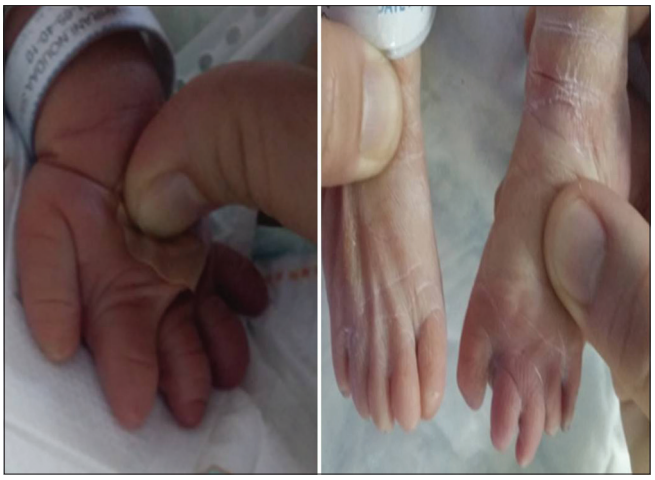

Figure 2: Brachydactyly of the fingers and toes

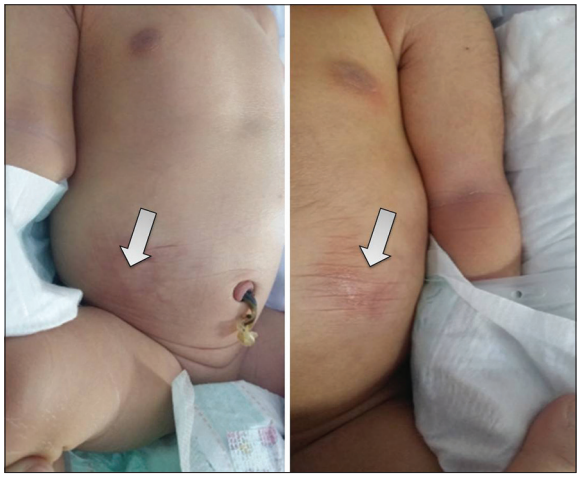

Figure 3: Localized cutis marmorata

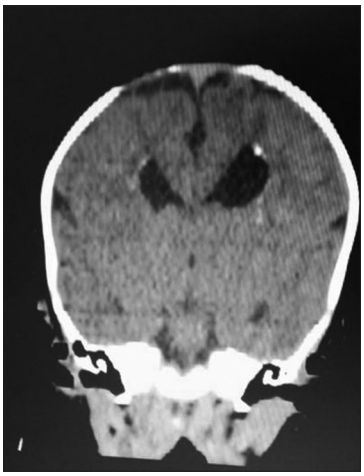

Figure 4: Computed tomography scan showing bone defect at both parietal and parasagittal bones

AOS carrying both the homozygous DOCK6 mutation c.1362_1365delAACT (autosomal recessive) and the heterozygous variant c.1963A>C in the DLL4 gene (autosomal dominant).

Discussion

AOS was initially described in 1945 by Adams and Oliver as combination of limb abnormalities and scalp defects.[5] Vascular, neurological, and congenital heart defects have been reported.[1] The clinical diagnosis of AOS depends on the presence of major and minor criteria. The major criteria include terminal transverse limb defects, aplasia cutis congenita, and family history of AOS. The minor criteria include cutis marmorata, congenital heart defects, and vascular anomalies. The presence of two major criteria or combination of one major and one minor criterion are sufficient for the diagnosis.[6] Our case has two major (limb defects and aplasia cutis congenita) and three minor criteria (cutis marmorata, cardiac defect, and vascular anomalies). The limb and scalp defects are typical clinical manifestations. The most frequently reported are syndactyly, brachydactyly, oligodactyly, polydactyly, and hypoplastic nails followed by scalp defect, generally in vertex area with or without underlying skull defect.[7] Reported ophthalmic involvement in AOS includes neovascularization of the retina, peripheral retinal ischemia, optic atrophy, and rarely retinal detachment.[8,9] Our patient had a rare presentation of bilateral retinal detachment associated with complete blindness, and sequelae consistent with the associated microvasculopathy reported in patients with the syndrome.[9]

To a large extent, AOS has an autosomal dominant mode of inheritance although autosomal recessive and sporadic cases have been reported.[10,11] As our patient had no family history of a similar condition, it can be considered as a sporadic one with unique genetic inheritance. In the past few years, mutations in six genes have been described as a cause of AOS [Figure 5]. NOTCH1, EOGT, and RBPJ are all members of the NOTCH signaling pathway. NOTCH signaling is activated by two families of ligands, namely, Jagged (JAG1 or JAG2) and Delta (DLL1, DLL3, or DLL4). Of these, DLL4 has an essential role in vascular development and angiogenesis, which places it as a

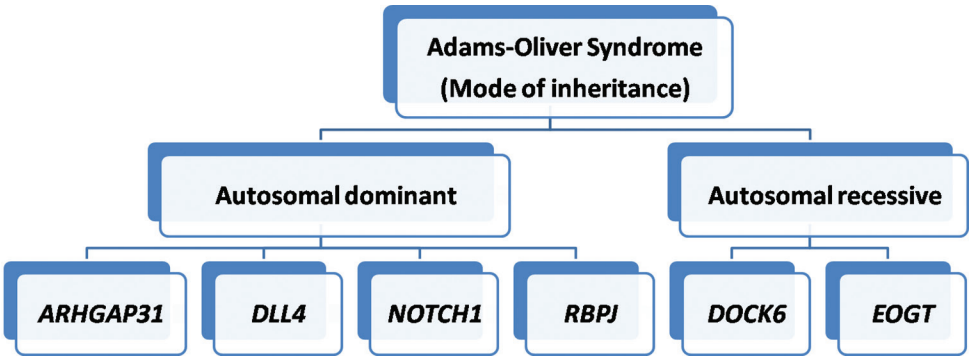

Figure 5: Mode of inheritance in Adams–Oliver syndrome

prime candidate for AOS, due to the presence of cardiovascular features in AOS-affected individuals.[12] Molecular genetic analysis in our patient showed a homozygous DOCK6 mutation c.1362_1365delAACT and a heterozygous missense mutation in DLL4 gene c.1963A>C leading to substitution of isoleucine by leucine at position 655 of the protein (p. IIe655 Leu); both findings were consistent with recently reported cases of the syndrome.[13-15] The patient uniquely carries both the homozygous DOCK6 (autosomal recessive) mutation and the heterozygous variant in the DLL4 gene which are transmitted as autosomal dominant trait of the syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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