Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 537–541

www.elsevier.com/locate/nmd

Case report

Lethal multiple pterygium syndrome: A severe phenotype associated with a novel mutation in the nebulin gene

Ebtesam Abdalla [a,*], Gianina Ravenscroft [b], Louay Zayed [c], Sarah J. Beecroft [b], Nigel G. Laing [b]

[a] *Department of Human Genetics, Medical Research Institute, University of Alexandria, Egypt*

[b] *Harry Perkins Institute for Medical Research and Centre for Medical Research, University of Western Australia, Nedlands, WA 6009, Australia*

[c] *Department of Obstetrics and Gynecology, Faculty of Medicine, University of Alexandria, Egypt*

Received 24 May 2016; received in revised form 21 November 2016; accepted 15 January 2017

Abstract

Fetal akinesia deformation sequence is a clinically and genetically heterogeneous disorder characterized by a variable combination of fetal akinesia, intrauterine growth restriction, developmental abnormalities such as cystic hygroma, hydrops fetalis, pulmonary hypoplasia, occasional arthrogryposis, and pterygia. The pathogenetic mechanisms of fetal akinesia deformation sequence include neuropathy, muscular disorders, neuromuscular junction disorders, maternal myasthenia gravis, restrictive dermopathy and others. We here report an Egyptian family presenting with recurrent lethal multiple pterygium syndrome. The diagnosis was based on antenatal sonographic demonstration of complete fetal akinesia and a large cystic hygroma with severe limb contractures evident on postmortem examination. Next generation sequencing performed on the second affected fetus identified a novel homozygous essential splice-site variant in the nebulin gene. In conclusion, our report adds further evidence for the involvement of the nebulin gene in the etiology of fetal akinesia deformation sequence/lethal multiple pterygium syndrome.

Keywords: Fetal akinesia; Lethal multiple pterygium syndrome; Nebulin gene

1. Introduction

Fetal akinesia deformation sequence (FADS) or Pena Shokeir syndrome is characterized by intrauterine growth retardation, contractures, craniofacial anomalies, limb anomalies, pulmonary hypoplasia and polyhydramnios and results from reduced movement *in utero*. A number of other fetal akinesia syndromes overlap phenotypically with FADS, including the lethal congenital contracture syndromes, multiple pterygium syndromes and arthrogryposis multiplex congenita. The clinical findings are dependent upon the time of onset of the akinesia, with earlier onset being associated with a more severe phenotype [1–3]. The unifying feature in all these disorders is reduced or absent fetal movement. Multiple joint contractures and subsequent pterygia are secondary consequences of diminished fetal movement, independent of the primary insult [2,4]. Fetal akinesias can result from primary defects involving any point along the motor system: motor neurons, peripheral nerves, neuromuscular junction and the skeletal muscle regulatory and contractile apparatus, and also the connective tissue [1].

Lethal multiple pterygium syndrome (LMPS; OMIM #253290) is a rare autosomal recessive genetic disorder with less than 30 families reported to date [5]. It is characterized by intrauterine growth retardation, multiple pterygia and flexion contractures causing severe arthrogryposis, and fetal akinesia. In severe cases, affected fetuses may develop subcutaneous edema, hydrops fetalis and cystic hygroma. Structural defects including cleft palate, cryptorchidism, pulmonary hypoplasia, diaphragmatic hernia, microcephaly, cerebellar and pontine hypoplasia can also be present [6].

The etiology of fetal akinesia deformation sequence/lethal multiple pterygium syndrome (FADS/LMPS) is heterogeneous. It is thought that more than half of the causes of fetal akinesia are of neuromuscular origin [7]. At least 30 causative genes have been identified, involving all points along the neuromuscular axis [8]. Defects in the embryonal acetylcholine receptor (AChR) were discovered to account for a significant

* Corresponding author. Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Building 9, Ground Floor, Jeddah 21589, Saudi Arabia. Fax: +966 12 6952437.

E-mail address: emnasr@kau.edu.sa; drebtesamabdalla@yahoo.com (E. Abdalla).

http://dx.doi.org/10.1016/j.nmd.2017.01.013

proportion of patients with LMPS and fetal akinesia [9]. More recently, mutations of the nebulin gene (*NEB*) have also been associated with LMPS [10,11]. Among the other genes involved in the etiology of neuromuscular fetal akinesias are *RYR1* [12], *GBE1* [13], *RAPSN* [14], *CHRND* and *CHRNA1* [15].

We here report the identification of a novel essential splice-site variant in the nebulin gene in a consanguineous Egyptian family presenting with recurrent FADS/LMPS.

2. Case report

An Egyptian pregnant female, married to her first cousin, presented with an abnormal second-trimester scan, and a history of a previous male fetus therapeutically aborted due to hydrops fetalis at 20 weeks of gestation. Postmortem clinical pictures were kept for the first fetus (Fig. 1A–C), while no DNA sample was available. The current pregnancy was also complicated by polyhydramnios and recurrence of the same fetal abnormalities. A detailed malformation scan, performed at 18 weeks of gestation, revealed a male fetus with growth restriction, fetal akinesia, a huge cystic hygroma, generalized skin edema, pericardial effusion and hydrothorax (Fig. 2). Flexion deformity of fetal extremities with lack of movements of the large joints was also observed. On the basis of the poor fetal prognosis, the parents opted for termination of the pregnancy. They consented for a fetal blood sample but declined muscle biopsies. Karyotyping showed a normal 46XY karyotype.

Postmortem clinical examination revealed a male fetus with growth retardation, huge cystic hygroma, generalized skin edema, particularly severe scalp edema, and all extremities were kept in a flexed position. The elbows were abnormally flexed and the hands showed camptodactyly with ulnar deviation of fingers. Multiple pterygia could be seen across all major joints and was predominantly striking at the neck to the extent that the chin was obscured by the marked anterior (chin to sternum) webbing. Dysmorphic facial features, including hypertelorism, downslanting palpebral fissures, long philtrum, and low set ears, were also noted (Fig. 1D–F).

A clinical diagnosis of fetal akinesia deformation sequence/lethal multiple pterygium syndrome was made.

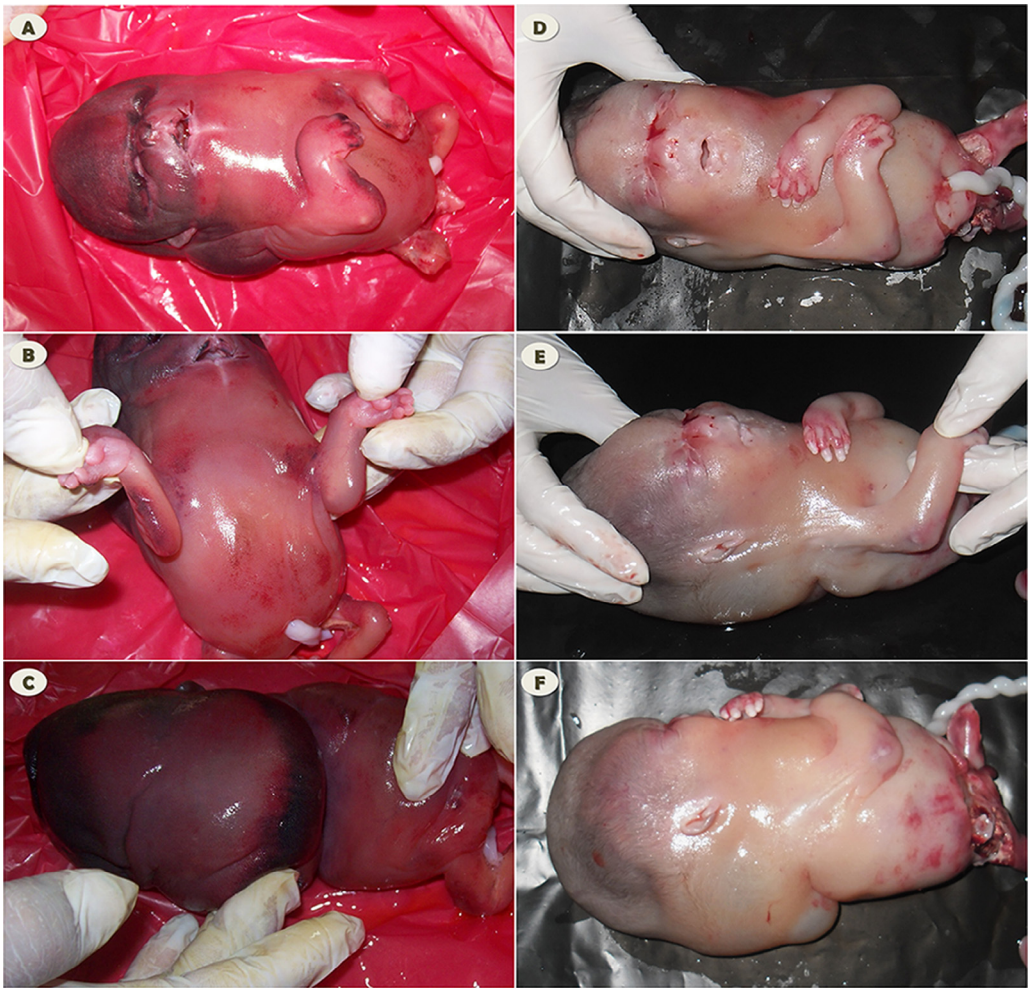

Fig. 1. Postmortem clinical photographs demonstrating the severe consequences of prolonged fetal akinesia in two sibling fetuses with lethal multiple pterygium syndrome. Dysmorphic facial features, including hypertelorism, downslanting palpebral fissures and long philtrum, striking anterior and lateral neck webbing, clenched hands with ulnar deviation of fingers, abnormally flexed elbows (A and D), multiple pterygia seen across all major joints (B and E), severe scalp edema and huge cystic hygroma (C and F).