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Neuromuscular Disorders 27 (2017) 947–950

www.elsevier.com/locate/nmd

Case report

Congenital myopathy due to myosin heavy chain 2 mutation presenting as chronic aspiration pneumonia in infancy

R. Tsabari [a], H. Daum [b], E. Kerem [a], Y. Fellig [c], T. Dor [d,*]

[a] Department of Pediatrics, Pediatric Pulmonology and Cystic Fibrosis Center, Hadassah-Hebrew University Medical Center Jerusalem, Israel
[b] Department of Genetics and Metabolic Diseases, Hadassah-Hebrew University Medical Center Jerusalem, Israel
[c] Department of Pathology, Hadassah-Hebrew-University-Medical-Center Jerusalem, Israel
[d] Neuropediatric Unit, Hadassah-Hebrew University Medical Center Jerusalem, Israel

Received 4 March 2017; received in revised form 24 May 2017; accepted 19 June 2017

Abstract

A 7-week-old infant presented with persistent noisy breathing and aspirations during swallowing. Neurological examination and brain MRI were normal. His 12-year-old brother underwent pneumonectomy at the age of 10 years due to recurrent aspirations leading to severe lung damage. The older brother developed subsequently ophthalmoplegia and nystagmus along with mild weakness of the neck flexors and proximal muscles. Exome analysis revealed homozygosity for a novel truncating mutation p.G800fs27* in the Myosin Heavy Chain 2 (*MYH2*) gene in both brothers, while parents and an unaffected sibling were heterozygous. A muscle biopsy from the older brother showed absence of type-2 muscle fibers and predominance of type-1 fibers. The aspirations causing pneumonia likely result from weakness of the laryngeal muscles, normally rich in type-2 fibers. The findings expand the phenotypic spectrum of *MYH2* deficiency. *MYH2* mutations should be included in the differential diagnosis of infants presenting with recurrent aspirations.

Keywords: Congenital myopathy; Aspiration pneumonia; Myosin heavy chain; MYH2

1. Introduction

Distinct isoforms of the myosin heavy chain are major components of muscle fiber types, determining its contractile and physiological properties. *MHC7* is a hallmark of type 1, slow fibers and cardiac muscle, while *MYH2* and *MYH1* are components of the fast, type 2a and type 2b fibers, respectively. Mutations in myosin heavy chain genes cause different myopathies, varying in phenotype according to the physiological role and expression pattern of the affected gene, and the severity of mutation [1]. The phenotype of people carrying *MYH2* mutations includes mild proximal muscle weakness, mildly weak neck flexors, ophthalmoplegia and ptosis [1]. Histologically, such patients show small or absent type 2 muscle fibers, and a predominance of type 1 fibers [1–3]. Thus patients presenting with these hallmark phenotypes are suspected to be carriers of *MYH2* mutations [4].

Aspiration pneumonia is a significant cause of pulmonary morbidity. It can be an acute event or a chronic recurrent syndrome caused by improper swallowing, or may occur due to gastroesophageal reflux. Chronic or recurrent aspiration may cause severe and even irreversible damage to lung tissue. However it has not been reported so far as the first manifestation of *MYH2* mutations.

Here we describe a pediatric case of recurrent aspiration resulting from a recessive mutation in the *MYH2* gene, causing a frameshift and presumably affecting the fast muscles of the larynx.

2. Case report

A seven-week old infant presented with noisy breathing and wet cough since birth, intensifying during feeds with episodes of choking and cyanosis. He is the third child of Muslim Arab, healthy and non-consanguineous parents. His birth weight was 3.2 kg after 41 weeks of gestation in which polyhydramnios was reported. His 12 year old brother who was followed up in a different hospital suffered also from dysphagia after birth and had gastrostomy at the age of one month and Nissen fundoplication at the age of 18 months. At the age of 4 years he was diagnosed with swallowing dysfunction due to upper esophageal sphincter dysfunction and underwent cricopharyngeal myotomy followed by botulinum toxin injections to the

* Corresponding author. Neuropediatric Unit, Hadassah-Hebrew University Medical Center Jerusalem, Israel.
E-mail address: talyad@hadassah.org.il (T. Dor).

http://dx.doi.org/10.1016/j.nmd.2017.06.015
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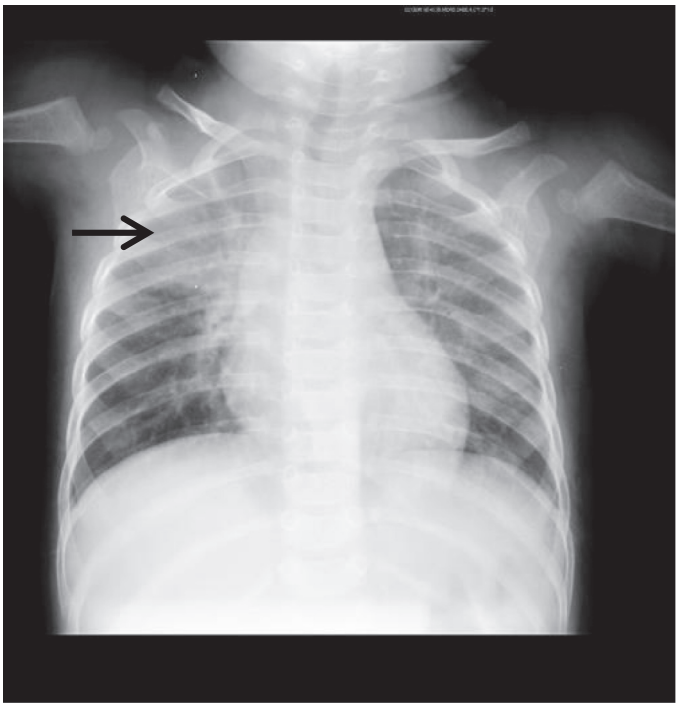

Fig. 1. Antero-posterior chest x-ray of the index patient, aged 7 weeks. Note right upper lobe opacities as a sign of aspiration pneumonia (arrow).

cricopharyngeal muscle. At the age of 10 years he underwent pneumonectomy due to recurrent pneumonia and chronic insults to the lung. He had normal motor, language and cognitive development, and subsequently developed ophthalmoplegia and nystagmus along with mild weakness of the neck flexors and proximal muscles.

The third child of the family is a healthy, 7 year old girl.

Physical examination of our patient including neurological examination was normal. He had a normal appearance and upper airway coarse breathing sounds. Because of the continuous noisy breathing, wet cough and episodes of difficult feeding, he underwent a dysphagia workup. Laboratory examination (complete blood count, electrolytes, glucose, liver function tests, kidney function tests and serum creatine kinase) was normal.

Chest X-ray demonstrated bilateral opacities especially in the right upper lobe (Fig. 1).

Flexible bronchoscopy illustrated a normal anatomy of the upper and lower airways, with accumulation of saliva in the larynx and lower airways.

Videofluoroscopy showed aspirations during swallowing (Fig. 2).

Esophageal pH monitoring for 24 hours and brain MRI were normal. Because of severe aspiration and reflux he had gastrostomy and Nissen fundoplication. Given the similar clinical phenotype of the two brothers, we suspected an underlying genetic disease and continued the work-up by exome sequence analysis.

2.1. Whole exome analysis (WES)

Exonic sequences were enriched from peripheral blood DNA using a kit (Agilent Technologies, USA). Sequences were determined by HiSeq2000 (Illumina) and 100 paired end bases were read. Read alignment and variant calling were performed with DNAnexus software using the default parameters with

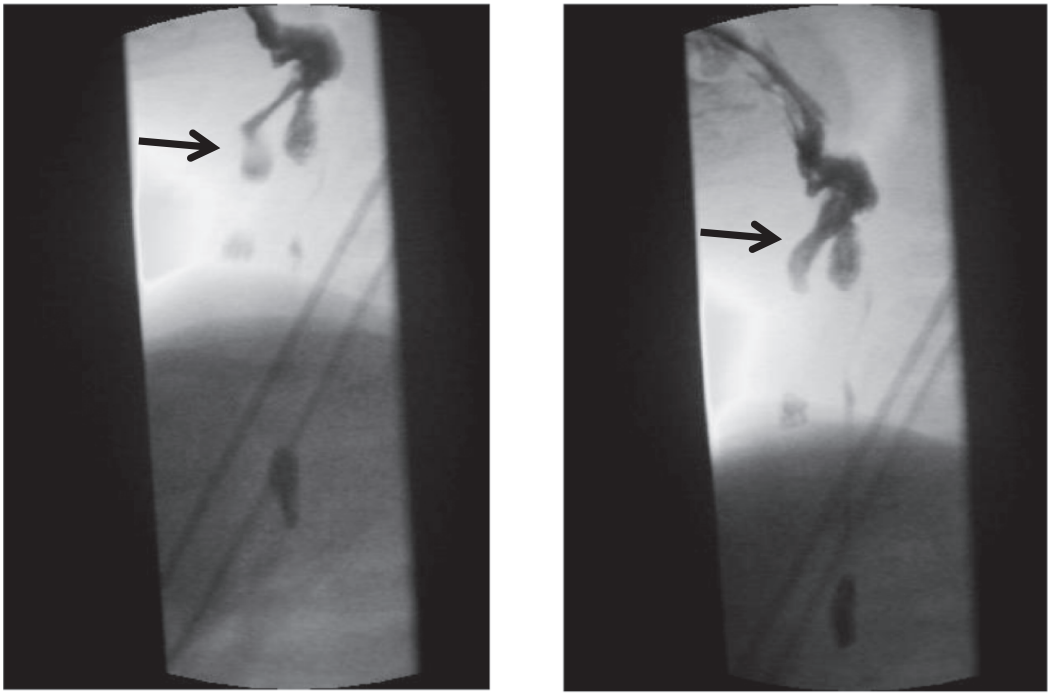

Fig. 2. Aspirations during swallowing as observed by video-fluoroscopy. Consecutive images from left to right of the index patient. Arrows indicate aspirations to the trachea.