A case of Emery Dreifuss Muscular Dystrophy with SYNE1 and SYNE2 mutations and white matter involvement

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Introduction

The Emery Dreifuss consists of early contractures, progressive muscle weakness and atrophy, and cardiac abnormalities. Various mutations of different genes are related with EDMD and the discovery of synaptic nuclear envelope genes *SYNE1* and *SYNE2*, encoding Nesprin-1 and Nesprin-2, respectively, were found to be associated with EDMD4 and EDMD5(1).

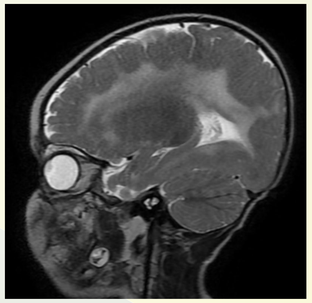
Nesprins belong to a family of giant KASH proteins, connect the nuclear envelope to the microtubule network and movement, contribute to nuclear envelope localization and structural integrity (2,3).

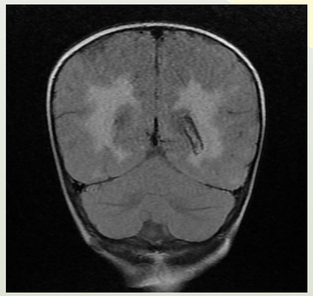
In this study we report an individual with both *SYNE 1* and *SYNE 2* mutation and neuroradiological findings of leukoencephalopathy. Also we summarize the clinical and molecular characteristics of previously reported Emery Dreifuss Muscular Dystrophy associated with nesprinopathies.

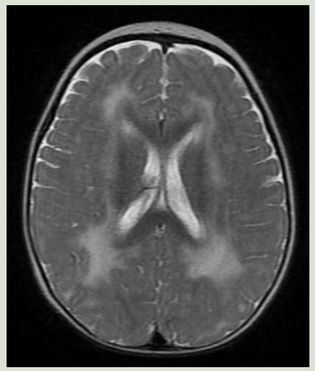
Case Report

The individual was 2 years old male with Syrian origin. There was no consanguinity between the parents. Her obstetric history was uneventful. At the age of nine-months-old he was admitted to our outpatient clinic with the inability to hold his head and sit. In the physical examination hypotonicity and contractures of the feet were detected; deep tendon reflexes could not be obtained in the lower extremities. Serum creatine kinase (CK) level was 3832 mg/dl. EMG revealed myopathic pattern and cranial MRI revealed white matter hyperintensity supporting leukoencephalopathy. In the neurological examination, who is now 2 years old, it was observed that he could sit without support but could not walk. There were scapular winging, contractures of the feet, and scapulohumeral and peroneal weakness. No cardiomyopathy was observed. His electrocardiogram showed incomplete right bundle branch block. He received physical therapy and rehabilitation support and his cognitive functions were evaluated as moderately retarded.

Congenital muscular dystrophy gene panel was revealed a heterozygous c.3046C>T (p.Pro1016Ser) missense variant in the exon 26 of *SYNE1* (NM_182961) and a heterozygous c.18723+14C>T intronic variant in the *SYNE2* (NM_182914). Detected variants were evaluated according to the guidelines of the American College of Medical Genetics and Genomics, c.3046C>T *SYNE1* variant (PM2, PP3) and intronic SYNE2 variant (PM2) were classified as Variant of unspecified significant (VUS).







Discussion

Nesprins are part of the nucleoskeleton and cytoskeleton complex and interconnects emerin and lamin (1). Impairment of this connection leads to Emery Dreifuss-like muscular dystrophies. Nesprinopathies is not understood enough because the full phenotypical spectrum is not well known yet. Up to now, the clinical range of nesprinopathies has been wider then known. Therefore, the diagnostic work-up should necessarily include a detailed description of the phenotypes of *SYNE1* and *SYNE2* mutations. Kölbel et al. denote to three different clinical phenotypes of *SYNE1* mutations; a myopathic type (EDMD4 with cardiomyopathy); an ataxic type and an arthrogrypotic type (4).

In animal studies, *SYNE1* and *SYNE2* double Kash deletions caused neonatal lethality and defects in brain development like enlarged lateral ventricles and laminary defects in the midbrain, brain stem in mice (5). Central nervous system involvement could be occur in nesprinopathies and cranial imaging should be necessary in evaluating a proband with nesprinopathy.

Our patient had heterozygous missense mutation in *SYNE1* and heterozygous intronic mutation in the *SYNE2* that in which that variant has not been previously reported. The heterozygous mutations have been linked to autosomal dominant EDMD4 and the accompanying mutation in the *SYNE2* gene may account for the severe clinic of the proband. Zhang et al postulated a dominant negative effect of the *SYNE* mutations, with the possibility of more severe manifestations in the compound heterozygote (1). In literature only one proband is defined with both *SYNE1* and *SYNE2* mutations with severe manifestations and our patient's severe clinic promote the idea of negative effect of compound heterozygote. Nesprins are involved in the pathogenesis of Emery Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. Future studies including further genetic screening of nesprins and cranial screening of EDMD associated with nesprinopathies, should lead to learn clinical and genetic features of the nesprinopathies.

References

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