

Congenital Muscular Dystrophy due to *POMGNT1* Mutation Presenting as Cardioembolic Stroke

Sir,

Congenital muscular dystrophy, structural eye abnormalities, and cobblestone lissencephaly form the triad needed to make a diagnosis of Muscle-Eye-Brain disease (MEB, OMIM 253280), an autosomal recessive disorder. They present very early in life with hypotonia, weakness, structural eye abnormalities, and brain malformation. Cardiomyopathy develops late in the course of the disease and may contribute to morbidity late in life. We herein report a 19-year old patient with MEB and cardiomyopathy who presented with a stroke, possibly due to embolism.

A 19-year-old boy, previously diagnosed with congenital muscular dystrophy (CMD) presented with a recent young stroke with left hemiplegia due to a right parietal, middle cerebral artery territory infarct. He had developmental delay since birth. Defective vision was noticed at two years and six months of age. Bilateral high myopia, glaucoma

and cataract were detected subsequently. He had a febrile seizure when aged five. Speech onset was at 3 years of age, with slow progression to phrases by 7 years. At 19 years, when questioned, he could barely answer in three-word sentences. Spontaneous speech was limited to voicing needs and uttering protests. He could comprehend simple one-step commands. Abstract thinking, mathematical ability, writing, reading, and reasoning were completely lacking. He could walk with support and was hyperactive. From early infancy, the mother noted weakness of all four limbs, with a proximal emphasis. Creatine phosphokinase values ranged from 300 to 5000 IU/L with a normal echocardiogram. His best-achieved motor milestone was walking with support. Magnetic resonance images (MRI) of the cerebrum revealed cobblestone lissencephaly in both frontal lobes and left occipital lobe, disorganized cerebellar folia with small cystic areas, an abnormal flattened pons, and ventricular enlargement. [Figure 1] This constellation of clinical

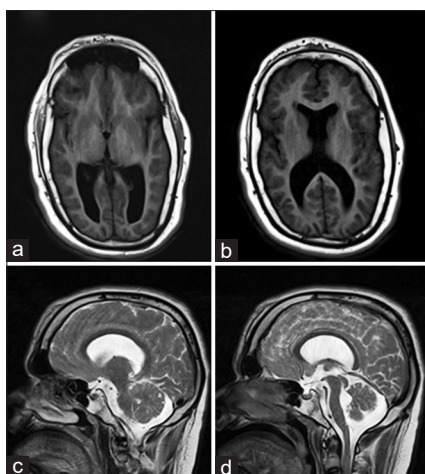


Figure 1: (a) Axial T1 W images showing cobble stone lissencephaly in the left occipital lobe. (b) Axial T1W images showing cobble stone lissencephaly in bilateral frontal lobes. (c) Sagittal T2W images showing disorganized cerebellar folia with small cystic areas – cortical dysplasia. (d) Sagittal T2W images showing abnormal flattened pons

and radiological findings suggested congenital muscular dystrophy with eye and brain involvement.

He was one of a sibship of three, with a normal brother and born of a nonconsanguineous marriage. The eldest sister had remained bedridden from the age of 2 and died of an unknown cause at 8 years and 6 months. There was no other affected family member.

When he now presented with stroke, in the setting of the muscle disease, a cardio embolic cause was suspected. Echocardiography revealed dilated left ventricle with severe global hypokinesia and an estimated ejection fraction of 30%, suggestive of dilated cardiomyopathy.

A clinical exome sequencing unfolded a pathogenic homozygous 3' splice site variation in intron seven of the *POMGNT1* gene (chr1:g. 46194653delT) that affects the invariant AG acceptor splice site of exon 8 (c.653-2del; ENST00000371992.1). The variant has not been reported in the 1000 genomes and gnomAD databases and has a minor allele frequency of 0.001% in the Medgenome internal database. The in silico prediction of the variant was damaging by Mutation Taster2.

We are reporting a young adult with stroke, cardiomyopathy, and congenital muscular dystrophy. Possibly his cardiac involvement could have been diagnosed earlier and cardioprotective drugs could have been given, so that his left ventricular dysfunction would not have become so severe.

One of the first studies on stroke in muscle diseases included 52 patients with Duchenne muscular dystrophy, 61 with myotonic dystrophy, and 14 with Becker muscular dystrophy followed up for up to 17 years. The prevalence of stroke in that cohort was only 1.5%.^[1] It is noteworthy that the population studied did not include Muscle-Eye-Brain disease. Among 665 patients with Duchenne muscular

dystrophy, stroke occurred in five (0.75%).^[2] All five had dilated cardiomyopathy, and one of them had atrial fibrillation. Cardiac involvement in muscle diseases may affect the cardiac conduction system or the myocardium. Cardiomyopathy has been reported to be rare in MEB.^[3] Among a series of 105 children with congenital muscular dystrophy, only seven had cardiac involvement. All patients in that cohort who had *POMGNT1* mutation had a normal cardiac and respiratory function.^[3]

CMDs have abnormally glycosylated dystroglycan. This group includes Walker-Warburg syndrome caused by mutations in *POMT1* and *POMT2*, MEB caused by mutations in (*POMGNT1*), Fukuyama CMD caused by mutations in *fukutin*, CMD type 1C caused by mutations in *FKRP*, and CMD type 1D secondary to mutations in *LARGE*.^[4-8]

Mutation in the *POMGNT1* gene can cause three different forms of muscular dystrophy. Type A3 is a severe congenital form with brain and eye anomalies, type B3 a less severe congenital form with impaired intelligence, myopia, optic atrophy, diffuse white matter changes, cerebellar cysts, and pontine hypoplasia, and type C3 presents with proximal muscle weakness, muscular hypertrophy, delayed motor development, myopia, and raised CPK. Possibly our child had type B3 as evidenced by the survival to the end of the second decade, cerebellar cysts, and pontine hypoplasia.

POMGNT1 mutation has also been seen in patients with nonsyndromic retinitis pigmentosa. Clement has reported a limb-girdle muscular dystrophy variant with onset at 12 years, normal intellect, and high myopia.^[9]

The brain MR imaging in children with *POMGNT1* mutation may show polymicrogyria, cobble stone lissencephaly, absence of septum pellucidum, frontal white matter hyperintensities, corpus callosum dysplasia, cerebellar hypoplasia, and cerebellar cysts.^[10]

Cobblestone lissencephaly is pathognomonic of diseases affecting alphadystroglycan, resulting in a disease affecting muscle, eye, and brain. The gray-white difference will not be seen, and there will invariably be dysmyelination. It is the neuronal over migration into the subarachnoid space disrupting the glia limitans, that gives the cobblestone appearance on the surface.

A new-born with a muscle disorder needs to be accurately diagnosed to aid in genetic counseling. Patients with Walker-Warburg syndrome may not survive long, and the chance for genetic labeling may be lost. A child with muscle weakness, with eye and/or brain involvement, in addition, has in all likelihood Walker-Warburg syndrome, MEB disease, or Fukuyama congenital muscular dystrophy. Further characterization is needed by next-generation sequencing to pinpoint the diagnosis. The interdisciplinary team managing the patient should essentially have a cardiologist, as cardiomyopathy by itself adds to morbidity and as illustrated by this case can lead to embolic stroke. If the involvement of cardiac muscle is recognized early, the natural history and rate of progression can probably be altered.

Patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's relative has given consent for clinical information other than patient's photograph to be reported in the journal. The patient and relatives 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.

Disclaimers

The views expressed in the submitted article are our own and not an official position of the institution.

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Conflicts of interest

There are no conflicts of interest.

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