Case report

Congenital mirror movements in a patient with alpha-dystroglycanopathy due to a novel POMK mutation

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Abstract

Dystroglycanopathies are a heterogeneous group of muscular dystrophies often associated with variable brain and eye involvement. Glycosylated alpha-dystroglycan (ADG) plays a key role in the development and stability of basement membranes as well as organizing axon guidance in the central nervous system. Congenital mirror movements, either isolated or in association with several genetic syndromes, are defined as inability to perform unimanual movements. We report an adolescent boy with limb-girdle muscular dystrophy due to ADG deficiency and coexisting congenital mirror movements. Genetic work-up revealed a novel homozygous missense mutation in the protein O-mannose kinase (POMK) gene. To our knowledge, this is the first patient in the literature with POMK mutation and congenital mirror movements.

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1. Introduction

Congenital mirror movement (CMM) disorder is a rare synkinesis form in which pathological involuntary movements on one side of the body occur simultaneously with intentional movements on the opposite side [1]. Mirror movements primarily involve the upper limbs, especially hands and fingers. Upper extremities are much more involved in fine motor skills due to a larger representation of hand motor area in the motor cortex. This phenomenon is mostly isolated or it may be in association with several genetic syndromes [2–5].

Alpha-dystroglycanopathies (ADG-pathy) include various forms of LGMD and CMD caused by defective function of ADG often associated with brain and eye involvement [6,7]. Alpha- and beta-dystroglycan are the major components of the dystrophin glycoprotein complex (DGC), which link the extracellular matrix to the actin-associated cytoskeleton [8]. Patients and animal models with defective glycosylation of ADG suggest that this protein is required not only for muscle maintenance, but also for peripheral-nerve myelination, neuromuscular-junction formation, neuronal migration in the brain, axon guidance, and development of eye, brain and other tissues. Defect in axonal guidance results in disturbances of neuronal migration/positioning [9].

To date, there are 18 identified genes associated with ADG-pathy, and many of them code for glycosyltransferases. POMK (protein-O-mannose kinase) encodes protein-O-mannose kinase, which is required for proper glycosylation and function of the dystroglycan complex [10]. POMK is a glycosylation-specific kinase, involved in the phosphorylation of M3 glycan Mannose on the C-6 position within the M3 O-glycan of alpha-dystroglycan. The M3 glycan seems to serve as the substrate recognition motif of POMK [11]. Laminin binding is also regulated by phosphorylation of the Man residue in the core M3 glycan [12,13].

Clinical spectrum of POMK mutations has been reported to be ranging a wide spectrum of severity, with different clinical manifestations ranging from WWS to LGMD [10,14].

Herein, we report a patient with limb girdle muscular dystrophy (LGMD) and CMM, with a novel homozygous missense mutation in POMK. To our knowledge, this is the first
patient in the literature with POMK mutation and congenital mirror movements.

2. Case presentation

A 17-year-old right-handed boy was referred with childhood onset muscle weakness, easy fatigue, clumsiness, and difficulty in running and climbing. He presented with a non-progressive muscle weakness, LGMD phenotype, with slow deterioration of muscle weakness from the age of 12 years. He was the first child of consanguineous parents, and he started to walk at 13 months. His parents recognized involuntary mirror movements of the hands in early infancy.

Physical examination at 19 years revealed short stature (158 cm, <3 p) and truncal obesity (67 kg, body mass index 27), mild learning difficulties, calf hypertrophy, proximal muscle weakness (MRC 4+/5), reduced deep tendon reflexes, Gowers sign, pes cavus deformity, and mirror movements in the upper limbs (Fig. S1 video link).

Serum creatine kinase level was 2400 IU/L and the echocardiogram showed normal heart function. Muscle biopsy performed at the age of 17 years showed mild dystrophic changes, with increase in internal nuclei, few degenerating and regenerating fibers and focal endomyal fibrrosis. Immunofluorescent analysis showed positive staining for laminin alpha 2 (Millipore), while alpha-dystroglycan staining (Millipore, VIA4) was negative. Dystrophin and sarcoglycans (a, b, g, d) were positive by immunohistochemistry (all Novocastra antibodies). Structural and functional magnetic resonance imaging (MRI/fMRI) and diffusion tensor imaging (DTI) were performed with a 3.0 Tesla magnet. Structural MRI showed cerebellar hypoplasia, cortical disorganization, brainstem hypoplasia, cerebellar cortical microcysts, and bilateral hippocampal incomplete rotation (Fig. 1a-c). Functional MRI with blood oxygen level–dependent imaging, obtained with a “high force hand clenching test” for 240 s and rest period, showed bilateral activation in the precentral gyri and supplementary motor areas during both an ipsilateral and a contralateral hand-clenching task (Fig. 1c-f). DTI fiber tracking showed a lack of decussation of bilateral corticospinal tracts at the medulla oblongata level (Fig. 1e).

The genetic work-up led to the identification of a novel homozygous missense mutation in the protein O-mannose kinase (NM_032237, exon 5, c.401T > G, p.V134G) by whole exome sequencing (NimbleGen V2 Exome Kit, 2 × 100 bp reads, ×80 coverage) after filtering for autosomal recessive inheritance as described elsewhere. This amino acid is conserved in homologs of POMK in vertebrate species in evolution down to Zebrafish [15].

3. Discussion

Congenital mirror movement is a rare and interesting phenomenon, which may persist into adulthood and is usually isolated. Dominant and recessive inherited mutations in a few genes (DCC, RAD51 and DNAL4) are known to be associated with CMM, which accounts for 35% of cases [1]. The products of these genes are involved in axonal guidance, pathfinding and development of corticospinal axons at the pyramidal decussation [1,16]. In relation to anatomic correlate, there are two primary hypotheses: a) fMRI data supported aberrant signaling across the corpus callosum, causing decreased interhemispheric inhibition of the contralateral motor cortex, and b) transcranial magnetic stimulation (TMS) studies supported either incomplete decussation of the corticospinal tract (CST) or abnormal distal branching of axons within the contralateral CST,
such that projections from the primary motor cortex synapse simultaneously on both ipsilateral and contralateral interneurons or motor neurons within the spinal cord [17,18].

Axon pathfinding is essential for the organization of proper neuronal connections during development [17]. Advances in neuroimaging and genomic technologies provide an increasing number of disorders that result from aberrant axonal wiring. Studies in murine models showed that two other enzymes required in the glycosylation pathway of dystroglycan, B3gnt1 and ISPD, act as regulators in axon guidance because dystroglycan (in its glycosylated form) plays a critical role in development of axon tracts, cue localization and axonal pathfinding due to a direct binding to the axon guidance via localization of Slit Guidance Ligand 1 (Slit) on the basement membrane [19]. The LG domain of Slit binds to the O-mannosyl-glycans of alpha-dystroglycan. It needs to be further investigated if POMK as well acts only as an indirect regulator of dystroglycan, Slit binding and subsequent axon guidance by phosphorylation of the Man residue in the core M3 glycan of dystroglycan or also by other yet unidentified functions of the protein. Dystroglycan is required for basement membrane integrity and commissural axon crossing in the developing spinal cord as it has been shown that dystroglycan mutant mice also show axon guidance defects [19]. In our patient, fMRI showed bilateral activation during hand-clenching tasks and DTI showed a lack of decussation of bilateral CST at the medulla oblongata level. The POMK gene (previously named sugen kinase 196-SGK196) is one of the recently known ADG-pathway genes and POMK is a glycosylation-specific kinase, involved in the phosphorylation of M3 glycan Mannose on the C-6 position within the M3 O-glycan of alpha-dystroglycan. This phosphorylation of Mannose on the M3 glycan is essential for the subsequent expansion of the glycan chain by the enzyme LARGE [13,20]. This extending glycan synthesized by LARGE consists of repetitive [glucuronic acid-[β1,3-xylene-α1,3]-] units and serves as binding partner for the LG4 domain of Laminin-alpha2 on the basement membranes [21]. Di Costanzo et al. reported that POMK was highly expressed in the human brain and muscle during early development [14]. Defective glycosylation of ADG leads to mislocalization of Slit and disrupts the Slit–Robo axis for axon guidance [19] thus causing abnormal development of corticospinal axons at the pyramidal decussation and might result in congenital mirror movements. Six individuals from four families with ADG-pathway due to POMK mutations were recently reported showing different clinical manifestations ranging from WWS to LGMD [10,14,22]. Our patient has LGMD and CMM with mild cognitive dysfunction.

In summary, we present a patient with LGMD and CMM, harboring a novel homozygous POMK mutation. To date, this association is reported in only one patient with congenital muscular dystrophy and ADG-pathway due to LARGE mutation [23]. Structural MRI of the patient reported in Ref. 23 showed abnormal neuronal migration, similar to that described in the cobbledstone complex, white matter changes, and hypoplastic brainstem. However, no functional studies (fMRI or DTI) were performed to demonstrate abnormal development of CST.

These individual observations, consistent with deep clinical phenotyping, provide clinical and molecular insights for understanding the underlying mechanism and may inspire future research for the treatment of these peculiar genetic disorders.

Ethical approval

Informed consent for publication and permission for use of photographs and videos was obtained from the patient. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with Helsinki Declaration of 1975, as revised in 2000.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2016.12.008.

References


