A Rare Cause of Autism Spectrum Disorder: Megaconial Muscular Dystrophy

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Abstract

Megaconial congenital muscular dystrophy (OMIM 602541) is defined by early-onset hypotonia, mildly elevated serum creatine kinase (CK) levels, muscle wasting, cardiomyopathy, psychomotor developmental delay and intellectual disability. The disease is caused by loss-of-function mutations in Choline kinase beta gene (CHKB) and has specific muscle biopsy findings. Here we investigate two patients with weakness of proximal muscles and generalized muscle atrophy, skin changes, aggressiveness, social communication and empathy difficulties. Both patients had mildly elevated serum CK levels. Whole exome sequencing (WES) performed for both patients and homozygous c.818+1G>A and homozygous c.1031+1G>A variants were detected in patient 1 and patient 2, respectively. We would like to draw the attention of autism spectrum disorder in early diagnosis of congenital muscular dystrophies.

Keywords: Autism, chkb, congenital muscular dystrophy, mitochondria

Background

Choline kinase beta gene (CHKB) encodes choline kinase beta enzyme which catalyzes the first step of phosphotidylcholine (PC) biosynthesis.[1] Loss of function mutations in CHKB gene produces Megaconial congenital muscular dystrophy (OMIM 602541) which is characterized by early-onset hypotonia, muscle wasting, proximal weakness, cardiomyopathy, mildly elevated serum creatin kinase levels, mental retardation, intellectual disability and behavioral changes.[2] The muscle biopsy reveals mitochondrial abnormalities and dystrophic changes. The center of muscle fibers is depleted of mitochondria, whereas at the periphery the mitochondria are markedly enlarged (Megaconia).[3] Here we report two patients with different mutations of megaconial muscular dystrophy and the clinical relevance of behavioral changes in the differential diagnosis among other congenital muscular dystrophy subtypes.

Case Report

Patient 1

A patient currently 9 years old girl was referred for investigation of delayed motor and social development at age of 3 years old. She was born after a normal pregnancy and delivery from a consanguineous parents, and her neonatal period was uneventful. Newborn screening tests for metabolic disorders were normal and she was properly vaccinated. She was able to sit independently at age of 12 months, stand independently at age of 24 months and walk independently at age of 48 months. Her walking ability was restricted to indoors due to muscle weakness and she never achieved the ability to rise from the floor unaided. Her receptive and expressive speech skills were delayed by 2 years of age, completely lost by 3 years of age. She had social communication and empathy difficulties, aggressive behavior, repetitive habits, impulsivity and hyperactivity, sensory overload and disruption of routines in her clinical history. Therefore she was diagnosed with autism spectrum disorder.

On physical examination; she had moderate weakness of the axial and proximal limb muscles with head lag (Medical Research Council grade 4/5 upper extremity proximals and 3/5 lower extremity proximals), She had reduced deep tendon reflexes and developed Gowers’ manoeuvre. There was no evidence of facial weakness, dysmorphic features, contractures and scapular winging. Her vision and hearing were normal.

Patient 2

A male patient, currently 8.5 years old, first presented to medical attention with delayed motor milestones and hypotonia at age of 1 year old. He was born after a normal pregnancy and delivery from a non-consanguineous parents and his neonatal period was uneventful. His motor development was delayed; he was able to control his head at age of 9 months, sit independently at age of

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isolation of dystroglycans and Dystrophinopathies. Diagnosis is frequent and important in patients with suspected megaconial muscular dystrophy. In the review of 15 patients of Mitsuhashi et al. in 2011; all patients were first described with mental retardation. In the next review of Mitsuhashi and Nishino in 2013; previous 15 patients were also described with intellectual disability in addition of 4 new patients which also had the same diagnosis. Haliloglu et al. investigated 15 patients with CHKB mutations in details; 5 of them showed autistic features, 2 of them had hyperactivity and 1 of them had sleep disturbances and the rest were normal. Also in the same review c.1031+1G>A mutation was detected in 4 patients, as our second case. Only one of them showed autistic features. Our patients showed autistic features at age of 2 years, later diagnosed with ASD and it was seen correlated with previous reports.

ASD relevance is not very rare in other neuromuscular diseases, which is also seen in alpha-Dystroglycanopathies and Dystrophynopathies. Alpha dystroglycanopathies...
consists of a spectrum of disorders: Fukuyama congenital muscular dystrophy, Walker Warburg syndrome and Muscle Eye brain disease; Merosin deficient CMD 1C and 1D; limb girdle muscular dystrophy 2I.[11] Brain MRI shows cortical malformation, white matter signal intensity changes and posterior fossa malformations in patients with alpha dystroglycanopathies, yet there are no radiological abnormalities which can explain intellectual disability in patients with CHKB mutations. Muscle biopsy findings (the center of the muscle fibers are depleted of mitochondria and enlarged mitochondria at the periphery) and mildly elevated CK levels makes the difference between dystrophinopathies and the patients with CHKB mutation.[8]

**Conclusion**
As we describe these two patients with megaconial muscular dystrophy due to different CHKB mutations; we would like to mark the significance of autism spectrum disorder in early diagnosis of congenital muscular dystrophies.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients 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.

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**Conflicts of interest**
There are no conflicts of interest.

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