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, agressiveness, 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 mithocondria, whereas at the periphery the mithocondria 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 musculer 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, agressive 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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12 months, stand independently at age of 24 months and walk independently at age of 60 months.

He showed intellectual and language impairment from age of 18 months. He had social interaction and communication difficulties, restricted interests, inability to imitate and lack of reciprocity. Self-destructive behavior and aggravation developed in time. He was diagnosed with autism spectrum disorder at age of 3 years.

Physical examination revealed muscle weakness affecting hip and shoulder flexors (MRC 4/5), diffuse generalised muscle atrophy, Gowers' manoeuver, hypoactive deep tendon reflexes, calf hypertrophy and ichthyosis. He had no facial muscle weakness, joint contractures, scapular winging and dysmorphic features. His vision and hearing were normal.

Laboratory investigations

In laboratory findings of both patients, creatine kinase (CK) levels were seen between 500 and 1000 IU/L (Normal 15-110 IU/L). The following investigations were normal: karyotype (including chromosome fragility studies), metabolic screen (urinary organic acids, plasma-urine amino acids, ammonia, thyroid function and very long chain fatty acids), liver function, cholesterol and triglycerides, carnitine and acylcarnitine mass tandem spectroscopy, uric acid.

Magnetic resonance imagining (MRI) and magnetic resonance spectroscopy of the brain was normal for both patients. Patient 1 had generalized tonic convulsion at age of 3 years and electroencephalography (EEG) tracing showed epileptiform activity. Epileptic pathology wasn't observed in routine electroencephalography (EEG) for patient 2. Patients were examined for electromyography (EMG), and electroneurography (ENoG). In electromyography (EMG), myopathic potentials were detected in all muscles explored (biceps, deltoid, medial gastrocnemius and vastus lateralis) while electroneurography (ENoG) findings were normal.

The echocardiographic (ECHO) evaluation showed dilated cardiomyopathy and decreased left ventricular systolic function for patient 1 while there was no abnormal ECHO findings for patient 2.

Muscle biopsy

Muscle biopsy of patient 1 taken at 3 years old and patient 2 taken at 1 year old, both showed variation in fiber size, increased number of internal nuclei and fatty infiltration. Oxidative enzyme reactions (NADH-TR and SDH) showed enlarged mitochondria at the periphery of most fibers. Immunolabeling of β-spectrin, dystrophin, dystroglycans (a and b subunits), calpain, sarcoglycans (a, b, g and d subunits), collagen 6, merosin/laminin-2, emerin, myotilin and laminin A/C were normal.

Genetic Results

For molecular diagnosis, we performed whole exome sequencing (WES) from DNA of the probands. DNA was isolated from peripheral blood using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA), according to the instructions of the manufacturer protocols. Before perfoming WES on the Illumina MiSeq platform we performed hybrid capture-based target enrichment using Nextera Flex for Enrichment (Illumina, Nextera DNA Flex Library Prep Reference Guide). The coverage was 95% for targeted sequences (mean coverage was >90% and 20× for 4 Gb; for exome panel). For analyzing variants we used Illumina VariantStudio desktop application and instructions for importing, annotating, and filtering variants.

In targeted sequences analysis, homozygous c.818+1G>A and homozygous c.1031+1G>A variants were detected in patient 1 and patient 2, respectively. These variations are located in intronic regions and nearby donor sites. To our knowledge, variants that altered the canonical AG or GT dinucleotides of the both donor and acceptor sites of splice sequences affect alternative splicing, and therefore both variants have a disruptive effect on protein function because of their localizations.[4] The c.818+1G>A and c.1031+1G>A pathogenic variants located in intron 7 and intron 9, respectively. While c.818+1G>A mutations is not defined in the literature, c.1031+1G>A mutation has been previously reported in 4 Turkish patients.[5] We planned to perform CHKB sequence analysis to parents and genetic counselling given to families.

Discussion

Megaconial muscular dystrophy is characterized by early-onset hypotonia, muscle wasting, proximal weakness, cardiac involvement (dilated cardiomyopathy, decreased left ventricular systolic function, congenital heart defects), seizures, EEG abnormalities, icthyosis-like skin changes, delay in gross-motor developmental milestones and expressive language skills, autistic features (echolalia, stereotypical hand movements), severe behavioral problems (self mutillation, sleep disturbances, aggressive behavior, attention deficit hyperactivity disorder).[2,5]

Autism spectrum disorder (ASD) prevelance is 7.2% in society.[6] This diagnosis is frequent and important in patients with suspected megaconial muscular distrophy. In the review of 15 patients of Mitsuhashi *et al*. in 2011; all patients were first described with mental retardation.[7] In the next review of Mitsuhashi and Nishino in 2013; previous 15 patients were described with intellectual disability in addition of 4 new patients which also had the same diagnosis.[8] 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 of the patients, as our second case. Only one of them showed autistic features.[5] Our patients showed autistic features at age of 2 years, later diagnosed with ASD and it was seen corelated with previous reports.

ASD relevance is not very rare in other neuromuscular diseases, which is also seen in alpha-Dystroglyconapathies and Dystrophynopathies.[9,10] 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 mithocondria 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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