Clinical and Genetic Spectrum of Dystroglycanopathy Due to *POMGNT1* Mutations in Russian Patients

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Objective. Dystroglycanopathies are the heterogeneous group of hereditary disorders, caused by the abnormal glycosylation of α-dystroglycan. The most common dystroglycanopathy is muscle-eye-brain disease (MEB) associated with mutations in the *POMGNT1* gene. MEB is autosomal recessive disease characterized by congenital muscular dystrophy, ocular abnormalities and brain malformation. The goal of the study is an analysis of clinical findings, laboratory features and results of instrumental research.

Methods. Molecular genetic diagnostics was performed using full exome sequencing. All patients and all parents were confirmed by Sanger sequinning.

Results. We observed 3 boys with MEB disease aged from 25 to 118 months, averaging about 7 years (83 months). The one patient had exceeded average values of height and weight at birth, two the other children had normal ranges. All children had severe motor development delay, only one patient could walk without support. Two older patients had mental retardation and lack of speech development. Language skills represented as vocalizations. Physical growth of our patients fluctuated from 3 to 75 percentiles for height and weight. The other clinical features include hypotonia and strabismus (all patients), autistic behavior (2 patients), ataxia, seizures, hepatomegaly (one in each patient). Dysmorphic features were non-specific.

Ophthalmological examination revealed congenital high myopia (2 patients), partial atrophy of an optic nerve (2 patient), nystagmus (1 patient), astigmatism (1 patient), retinal atrophy (1 patient).

Biochemical analysis showed elevated creatine kinase from 1874 to 6266 (averaging 3754 U/L), ALT from 42 to 93(68 U/L), AST from 53 to 106 (80 U/L), LDH from 370 to 503 (437 U/L).

Electromyographic examination has showed that all children had signs of primary muscle lesion. Muscle MRI has displayed a severe atrophy muscles and fatty infiltration in one patient. MRI findings have reported pachygyria and ventriculomegaly (all patients), hypoplasia cerebellum, corpus callosum, pons (2 patients), hypoplasia of temporal lobes (1 patients), cerebellum cysts (2 patients). EEG did not reveal epileptic form activity.

We revealed compound heterozygous mutations in all three patients. These were five different mutations: missense c.385C > T (p.R129W) and c.1325G > A (p.R442H), nonsense c.643C > T (p.R215X), splicing c.1539+1G > A and frameshift duplication c.453_456dup (p.S153Vfs*5). The last one was not previously described in the HGMD database.

Conclusion. Clinical and genetic features were described in Russian patients with dystroglycanopathy due to *POMGNT1* mutations.