Clinical Features Beyond Myopathy: Three Calpainopathy Patients with CAPN3 Mutation

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OBJECTIVES

Calpainopathies are caused by pathogenic variants in the calpain-3 gene (*CAPN3*). LGMD-1 (previously symbolized LGMD2A) is more common and inherited autosomal recessively. LGMD-4 (previously symbolized LGMD1I) is the autosomal dominant form and have a phenotype that resembles but is generally milder than the recessive type. Heterozygous mutations in the *CAPN3* gene have been reported in some patients with idiopathic generalized epilepsy and without muscle involvement. Thus far, 2 patients with calpainopathy accompanied by epilepsy have been reported. First patient was a 14-year-old girl with biallelic mutations in the *CAPN3*, and second patient was a 12-year-old boy diagnosed as partial calpain deficiency by Western-blotting of muscle protein. Calpain 3 is a calcium-dependent protease which is mainly located in skeletal muscle even though calpain-3 RNA was also detected in brain tissue. The activation of calpain by the influx of intracellular calcium through NMDA receptors activates AMPA receptors by splitting GluR1 component, resulting in inhibition of excitatory ion flow; this dysfunction of AMPA receptors in patients with mutations in *CAPN3* could be related to the pathophysiology of epilepsy. We aimed to present the extramuscular clinical findings of 3 patients with the diagnosis of calpainopathy.

MATERIALS & METHODS

The data of the cases were obtained retrospectively from the pediatric neurology records of Kocaeli University Faculty of Medicine.

	Case 1	Case 2	Case 3
Genetic Analyses	c.1621C>T homozygous variant in *CAPN3* gene	c.1621C>T homozygous variant in *CAPN3* gene	c.1303G>A heterozygous variant in *CAPN3* gene
Age-Gender	4 y, male	5 mo., female	7 y, male
Proximal muscle weakness	Yes	Yes	Yes
Epilepsy	No	Yes	Yes
Dysmorfic facial features	No	Yes	Yes
Cognitive impairment	No	Yes	Yes
Other organ abnormalities	No	ASD, PDA, left ectopic kidney	No
Brain abnormalities	No	microcephaly, thin corpus callosum and bilateral basal ganglia changes consistent with chronic ischemia	diffuse calvaria thickening
High CK levels	Yes	Yes	No

Table 1. : Clinical features of three patients with Calpainopathy

RESULTS

Case 1 was a 4-year-old boy and presented for evaluation of high serum CK at the ages of 4 years. Case 2 was sister of case 1, and she was first evaluated for high CK at 5-month-old. Their parents were first degree cousin. Both siblings had proximal muscle weakness, Gower's sign and high CK levels. Case 1 had behavioral abnormalities, and case 2 had intellectual disability, behavioral abnormalities, cardiac abnormalities (ASD, PDA), left ectopic kidney, and focal seizures. Case 2 had dysmorphic features such as triangular face, upturned palpebral fissures, deeply located eyes, prominent suborbital lines and nasal root, low hanging columella, micrognathia and pes cavus. Her cranial MRI findings were compatible with microcephaly, thin corpus callosum and bilateral basal ganglia changes consistent with chronic ischemia. Chromosom analysis and array CGH were normal. WES analysis of the siblings showed homozygous, pathogenic variant in the *CAPN3*, and the patients diagnosed as AR LGMD-1 calpainopathy. Parents were heterozygous for the same variant.

Case 3 was a 7-year-old girl presented with intellectual disability, behavioral abnormalities, short stature, and obesity. Her phenotype was similar with Prader-Willi syndrome, but this syndrome was excluded by genetic testing. Cranial MRI revealed diffuse calvaria thickening. Her serum CK was normal. WES analysis showed heterozygous, pathogenic variant in *CAPN3*, and AD LGMD-4 was diagnosed. Muscle biopsy confirmed genetic result.

CONCLUSIONS

CAPN3-related calpainopathy is a type of limb-girdle muscular dystrophy, but extramuscular clinical findings may become prominent more than muscle findings.

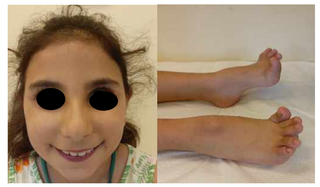

Figure 1. Case 2's phenotype and her pes cavus deformity

KEYWORDS

calpainopathy, intellectual disability, epilepsy