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Case Report

Familial association of genetic generalised epilepsy with limb-girdle muscular dystrophy through a mutation in *CAPN3*☆

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1. Introduction

Muscular dystrophies are a heterogeneous group of inherited diseases that cause progressive muscle weakness. The association of epilepsy with some of these diseases has been previously described and has most commonly been found for Fukuyama-type muscular dystrophy due to alterations in cerebral neuronal migration [1]. Among muscular dystrophies, limb-girdle muscular dystrophies (LGMDs) represent the fourth most common group, with a prevalence of 1.63 per 100,000 individuals [2]. The diseases in this group share a common phenotype involving progressive weakness of the scapular and pelvic girdles that starts after 2 years of age and can be accompanied by different degrees of elevation in blood creatine kinase (CK) levels and by various anatomic pathological findings. LGMDs are subdivided into LGMD1 and LGMD2 depending on whether the inheritance is dominant or recessive, respectively. LGMD2A, which is caused by deficiency of the calpain 3 protein owing to mutations in the *CAPN3* gene, is the most common form of LGMD in Europe and America [2]. Its association with epilepsy has been described in only two isolated cases [1,3], both of them on the spectrum of genetic generalised epilepsies (GGEs). The latter are the most common group of epilepsies with genetic aetiology, accounting for 15–20% of all epilepsy cases [4]. Nonetheless, none of the genes usually involved in monogenic epilepsies seem to play a major role in GGE, probably indicating a polygenic predisposition to GGE and therefore a complex inheritance pattern [5]. Here, we describe a family in which a case of LGMD2A is combined with cases of epilepsy having a GGE phenotype in the context of a *CAPN3* mutation.

2. Clinical cases

Fig. 1 shows the pedigree of the family. We performed genetic analyses on the third generation and one subject of the second generation.

2.1. Subject 1

Subject 1 is a 25-year-old male with a juvenile myoclonic epilepsy (JME) phenotype. He exhibited normal psychomotor development but started having epileptic seizures, including generalised tonic–clonic seizures (GTCSs), myoclonic seizures, and sporadic absence seizures, at 16 years of age. He did not present muscular symptoms, and CK levels were normal. Structural alterations were not present on cerebral magnetic resonance imaging; on the electroencephalogram (EEG), generalised spike and wave discharges were observed. The patient received treatment with valproic acid (VPA), which has maintained sporadic frequency of myoclonic seizures. The patient is heterozygous for a frameshift mutation c.2362_2363delinsTCATCT in exon 22 of the *CAPN3* gene.

2.2. Subject 2

This subject is a 24-year-old man who had normal psychomotor development and is presently asymptomatic, with normal CK levels. At age 10, he experienced two GTCSs; after the second, he started treatment with VPA, which was continued for 4 years. The treatment was discontinued before the disappearance of seizures, and there was no subsequent recurrence of the seizures. In this study, alterations were not detected by cerebral computed tomography scans, but generalized interictal epileptiform discharges were noted on several EEGs. The patient is heterozygous for the frameshift mutation c.2362_2363delinsTCATCT in exon 22 of the *CAPN3* gene but has no muscular symptoms.

2.3. Subject 3

Subject 3 is an 18-year-old woman free of both muscular symptoms and epileptic seizures. She does not have the familial mutation in the *CAPN3* gene.

☆ **Declarations of interest:** None.

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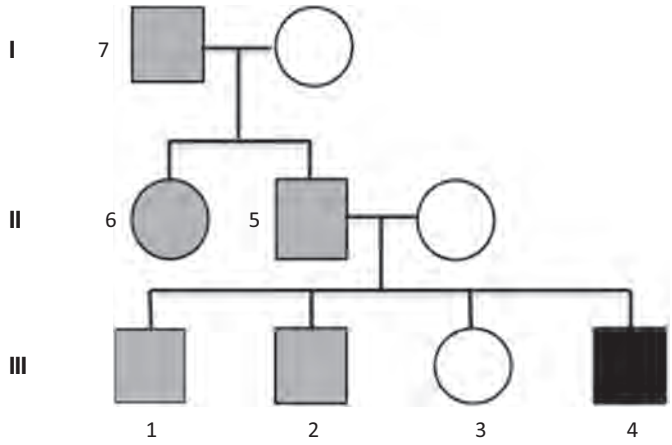

Fig. 1. Pedigree of the studied family. Grey colour represents an epilepsy phenotype. Black colour denotes the LGMD2A phenotype.

2.4. Subject 4

This subject is a 16-year-old male with the LGMD2A phenotype. He showed normal psychomotor development, but at the age of 9, he began manifesting clinical weakness of the pelvic girdle, tiptoe walking, slight lumbar hyperlordosis, difficulty walking on his heels, and a positive Gower's sign. He had elevated CK levels (6426 UI/L, reference range 0–171). He has not manifest with seizures thus far. He is homozygous for the frameshift mutation c.2362_2363delinsTCATCT in exon 22 of the *CAPN3* gene.

2.5. Other members of the family

Subjects 5, 6, and 7 – the father, paternal aunt, and paternal grandfather of the above-mentioned subjects, respectively – have epilepsy. Subjects 5 and 6 are 53 and 55 years old, respectively; they have a well-controlled form of GGE with isolated GTCSs, both are seizure-free due to treatment with VPA. They have not developed muscular symptoms, and CK levels have been normal or slightly elevated in different measurements in both subjects (between 135–193 and 145–197 UI/L, respectively). Subject 5 is heterozygous for the familial mutation. Nevertheless, we do not have other clinical or genetic data on subjects 6 and 7.

3. Discussion

LGMD2A, or calpainopathy, is one form of LGMD that until now has been associated with epilepsy in only two cases [1,3]. The first case was that of a 12-year-old boy with the LGMD phenotype in whom a partial calpain deficiency was found by western blotting of muscle protein; at age 7, the boy developed typical absence seizures with generalized spike–wave discharges at 3 Hz on the EEG and was treated with ethosuximide, which provided good seizure control. The boy had no family history of epilepsy, but two of his sisters showed muscle involvement [1]. The second case was that of a 14-year-old girl with clinical signs of girdle muscle weakness and two heterozygous mutations in the *CAPN3* gene (the missense A2288G mutation and the 100delG deletion in codon 763); at the age of 13, she experienced absence seizures and showed typical generalized epileptiform discharges on an EEG. The girl was successfully treated with VPA. In this case, the patient's sister also presented with epilepsy with absence seizures and GTCSs but had not experienced muscle involvement and had not undergone genetic analysis [3].

Here, we described several members of a family with a *CAPN3* mutation that gave rise to the LGMD2A phenotype in a single homozygous subject and is also associated with epilepsy in several family members, including three subjects who are heterozygous for the known mutation. The epilepsy type of these three subjects can be categorized as GGE: one subject has a clear JME phenotype, and two subjects have GGE with isolated GTCSs. The mutation present in this family (frameshift c.2362_2363delinsTCATCT in exon 22) has been described [6]. It is possible that the coexistence of the mutations in the *CAPN3* gene and epilepsy are coincidental. Nonetheless, there are some data suggestive of a possible association. On the one hand, the subjects with epilepsy and a mutation in the *CAPN3* gene have the phenotype of a specific epileptic syndrome, GGE, in common. In addition, among the subjects studied by genetic analysis, the only one who has not developed epilepsy does not have the heterozygous mutation, with the other three known heterozygous subjects having developed GGE. These two findings, although they are not direct evidence, point to a possible relation between *CAPN3* mutations and GGE. On the other hand, given the high prevalence of GGE [5], another possibility is the casual relation between these two genetic entities in the same family, with the known mutation causing only the LGMD phenotype in subject 4.

As mentioned above, GGE has a complex inheritance pattern involving multiple genetic factors. In addition, environmental factors probably also play a role in GGE pathogenesis, and this situation can lead to phenotypic variations among members of the same family [5]. This could be the case for the family studied in the present work where we observed different GGE phenotypes: from a JME phenotype to the phenotype of GGE with GTCSs and benign evolution that remains in remission without treatment. In the genetic complexity of GGE, susceptibility variants at different loci have been documented [5]. Thus far, it has not been proven that the chromosomal 15q15.1 region – the location of the *CAPN3* gene, which encodes calpain 3 and is responsible for LGMD2A when mutated – is related to genetic epilepsy. Calpain 3 is a calcium-dependent protease located mainly in mammalian skeletal muscle; however, the presence of calpain 3 mRNA has also been detected in other tissues, including brain tissues, and in cells with a neuronal phenotype [7,8]. The activation of calpain by the influx of intracellular calcium through NMDA receptors cleaves the GluR1 domain of AMPA receptors, resulting in inhibition of excitatory ion currents [9]; this regulatory function of AMPA receptors may be aberrant in patients with mutations in *CAPN3* and could thus be related to the pathophysiology of epilepsy. Nevertheless, there is currently no clear evidence regarding the possible participation of calpain 3 in epilepsy, particularly at the level of the central nervous system, and to date, reports linking a deficiency of this protein to LGMD2A with epilepsy have been rare. Therefore, future reports of new cases and an expansion of the body of knowledge about calpain 3 physiology and the genetics of GGE are necessary for further research into this association.

4. Conclusions

We presented a unique case of a family in which LGMD2A is associated with GGE. Despite the possibility of a serendipitous link, we believe that it is important to report all cases that relate these two conditions to elucidate their possible association and to test the hypothesis that mutations in *CAPN3* are some of the many predisposing factors related to the complex genetic aetiology of GGE.

Ethical statement

We wish to confirm that this work has been carried out in accordance with the Declaration of Helsinki.

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