A case of CAV3 caveolinopathy / channelopathy with familial absence epilepsy and distal myoneuronopathy extending the clinical spectrum

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INTRODUCTION

Although Caveolin-3 (encoded by the CAV3 gene) is predominantly expressed in skeletal and cardiac muscles, it is also expressed in Schwann cells and the brain. Mutations in CAV3 are associated with many different muscular and cardiac disorders, such as Limb-Girdle Muscular Dystrophy Type 1C, Idiopathic HyperCKemia, Inherited Rippling Muscle Disease, Distal Myopathy, Familial Hypertrophic Cardiomyopathy, Arrhythmogenic Long QT Syndrome and Sudden Infant Death Syndrome. In addition, muscle cramps, myalgia, and myotonia have been linked to “Caveolinopathies”. The T78M Cav-3 variant has been associated with both skeletal and cardiac muscle pathologies. Caveolin-3 binds several proteins including ion channels and modulates their functional properties through this interaction. Alteration of caveolar domains significantly affects the properties of cardiac Hyperpolarization-Activated Cyclic Nucleotide–Gated Channel 4 (HCN4), Kv1.5, Cav1.2 and Nav1.5 channels.

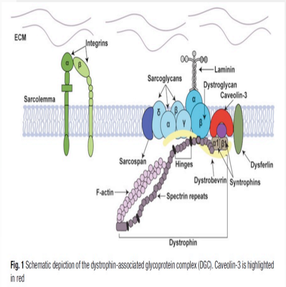

Fig. 1 Schematic depiction of the dystrophin-associated glycoprotein complex (DGC). Caveolin-3 is highlighted in red

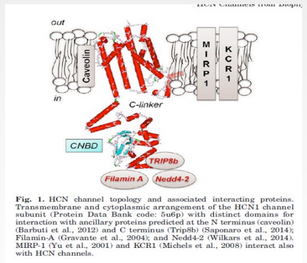

Fig. 1. HCN channel topology and associated interacting proteins. Transmembrane and cytoplasmic arrangement of the HCN1 channel subunit (Protein Data Bank code: 5u6p) with distinct domains for interaction with ancillary proteins predicted at the N terminus (caveolin) (Barbuti et al., 2012) and C terminus (Trip8b) (Saponaro et al., 2014); Filamin-A (Gravante et al., 2004); and Nedd4-2 (Wilkars et al., 2014). MiRP-1 (Yu et al., 2001) and KCR1 (Michels et al., 2008) interact also with HCN channels.

OBJECTIVES

We present a case with the coexistence of distal myoneuronopathy and familial absence epilepsy with pathogenic CAV3 mutation to draw attention to extremely rare diseases with a variable clinical spectrum called CAV3 caveolinopathies.

CASE

15-year-old male patient

Complaint

- Gait disturbance that began at age 11 and getting worsened, prominent in left foot
- Nocturnal urinary incontinence

History

- Diagnosed with absence epilepsy at age 3
- Drug-free
- Mother with childhood epilepsy
- Two brothers and an uncle with idiopathic generalized epilepsy

Examination

- The hammering of the toes, pes cavus deformity
- Resting tremor in hands
- Hypoactive deep tendon reflexes
- Difficulty walking on tiptoe

Investigations

- CK: 265 U/L
- Brain and spinal MRI: Normal
- ENMG: Compatible with motor neuron disease
- WES: A *heterozygous p.T78M (c.233C>T) (NM001234.5)* mutation in the *CAV3 gene*
- The same heterozygous mutation was found in the CAV3 gene in the mother and two brothers.

DISCUSSION

Milone et al., reported a patient who had a heterozygous transition c.169G>A (p.V57M) mutation of CAV3 with myalgia, muscle stiffness, fatigue, myotonia and generalized epilepsy. Since genetic testing for CLCN1, SCN4A DM1, DM2 and karyotype analysis were all normal. CAV3 mutation is the only known pathogenic abnormality associated with myotonia in their patient. However, they could not prove the CAV3 mutation is the cause of the electrical myotonia. They thought that a novel as yet unidentified channelopathy may be the cause for both epilepsy and myotonia, but a channelopathy affecting the brain and muscle and causing myotonia selectively in the gastrocnemius seems less likely. Therefore, they considered myotonia and epilepsy as independent coincidental diseases and explained the myotonia by increased membrane excitability due to mutated Cav-3 interfering of the sodium channel.

Caveolin-3 is a lipid raft component of myocyte membrane that colocalizes with and affects the expression and function of HCN channels, as well as their susceptibility to modulating signals. HCN channels play important roles in modulating cellular excitability, rhythmic activity, dendritic integration and synaptic transmission. The evidence for HCN mutations in human epilepsy has been reported in recent years. Different variants of HCN4 have been identified in patients with different subtypes of generalized epilepsy. The HCN channels interact with accessory proteins as CAV3 that finely regulate the function of If/HCN4. (Figure 1). HCN4 expression was found remarkably higher throughout human cardiac tissue than in the brain. Afterward, HCN4 was detected also in other tissues, such as the thalamus and testis. Campostrini et al., previously reported p.Thr78Met variant of CAV3 to be found at a higher frequency in patients with cardiac arrhythmias by affecting HCN4 current compatibly with the high expression of caveolin-3 in the heart. DiFrancesco et al., identified p.Thr78Met variant of CAV3 in unrelated 7 cases of 597 epileptic patients and 6 of 7 are affected by generalized epilepsy. Since Caveolin-3 both expressed in muscles and brain and affects HCN4 ion channels which is related with seizure and hyperexitability in myocyte. We speculate both epilepsy and neuromuscular disorder of the case of Milone et al., and our case may be caused by CAV3 mutation. Since the repeated ENMG’s were consistent with lower MND and CK was normal, we also speculate that lower MND may be associated with CAV3 mutation.

CONCLUSIONS

CAV3 gene mutations have been observed to cause different caveolinopathies in different individuals. It is not yet clear why a particular CAV3 gene mutation can cause different patterns of signs and symptoms, even within the same family. Similarly, the present case and brothers with generalized epilepsy all had CAV3 mutation. However, only the proband had myoneuronopathy and none of the family members with CAV3 mutation had cardiac arrhythmia. Future studies should try to explain the possible underlying mechanisms for both epilepsy and lower MND by focusing on exploring the specific neuronal subtypes, neuroanatomical location and distribution patterns of each identified pathogenic variant.

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