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Single nucleotide variants in the SCN1A gene and their relation to the development of type 3 familial hemiplegic migraine

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Introduction

Migraine is a complex brain disorder that is influenced by different pathophysiological aspects such as inflammation, structural changes, and dysfunctions in multisensory processing. Recent studies have showed that possible mutations in genes that interfere with the excitability of ion channels linked to nociception are one of the key mechanisms for the development of a migraine. In this sense, it is known that familial hemiplegic migraine type 3 (FHM3) undergoes specific missense mutational influences on the SCN1A gene that encodes the a1 subunit of NAV1.1, a voltage-gated sodium channel present in the brain that demonstrates that the deregulation of the excitatory- inhibitory balance of these channels in specific circuits may come to characterize the pathogenic mechanism of FHM3.

Objectives

Investigate the relation of single nucleotide variants (SNVs) on the SCN1A gene encoder of the a1 subunit of the NAV1.1 channel with the development of FHM3.

Methods

Narrative review performed by active search in the digital databases Virtual Health Library (BVS), PubMed, SciElo and Google Scholar.

Development

Migraine pathophysiology involves the distribution of ions between intracellular and extracellular compartments, which shows the role of the ion channels in the disease. In this regard, there is an activation of the trigeminal vascular meningeal system by the NaV1.1 channels, which are expressed in Aδ fibers. Therefore, it is believed that mutations on genes that encodes the ion channels act in the development of migraine, mainly by the meninges, as they are densely innervated by trigeminal nerve endings.

Migraine can be classified by the presence or absence of aura, and the FHM – clinical condition and genetically heterogeneous, transmitted in an autosomal dominant form – presents aura. Among the types of FHM, the type 3 comprises mutations on gene SCN1A – located on chromosome 2q24 and responsible for the encoding of proteins involved in ion transport -, these genetic alterations are considered triggering factors for this type of migraine. This gene is responsible for encoding the a1 subunit of the voltage-gated neuronal sodium channels NaV1.1, whose function is mediate the permeability of excitable membranes in the central nervous system. Thus, different mutations with gains of function (L1670W, L263V, L1649Q, e Q1478K) in the SCN1Agene, stimulate the nociceptive activations and, thereafter, the increase of severe migraine pain.

Results

FHM shows a dominant autosomal pattern with penetrance of 70% to 90%. The mutations related to FHM type 3 cause gain of function on NAV1.1 channels, and hyperexcitability of GABAergic neurons. The increased concentration of extracellular potassium is consequence of GABAergic interneurons hyperexcitability and this has been proposed as a possible mechanism of cortical depression in FHM3. The SNVs activity with gain of function increased nociceptive spikes, suggesting that the excitability of afferent meningeal terminals was increased. SNV L263V is much more effective on causing firing and spikes then the other variants. SNV L263V, on SCN1A gene, is characteristic of epilepsy and it was also the first SNV to be associated with FHM. In a Portuguese family, researchers found the first case of hemiplegic migraine and epilepsy. It was identified as a missense SNV that changed a single nucleotide in exon 6, that caused the substitution of Leucine to Valine at the position 263 of the NAV1.1 a1 subunit. This result reveals that FHM and epilepsy can share, at least partially, the same genetic pathway.

Conclusion

In conclusion, there are alterations in the ion channels when it comes to FHM type 3, because individuals with this disease showed changes in the SCN1A gene of the SNV type. SNVs in this gene must alter permeability leading to hyperexcitability and consequent nociceptive activation, causing the episodic migraine pain.

Keywords: Migraine with aura, NAV1.1 Voltage-gated sodium channel, Trigeminal nerve, Ion transport.