MIGRAINE AS A CHANNELOPATHY

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Migraine is the most prevalent brain disorder, affecting at least 12% of the general population, females threefold more frequent than males, and costing the EU annually € 155 billion (WHO 2011). The disease is typically characterised by recurrent disabling attacks of one to three days of severe headache, nausea, vomiting and phono-and photophobia. In one third of patients attacks may be accompanied by neurological, often visual, aura symptoms. Fifty percent of patients have attacks at least twice a month and ten percent at least weekly. Migraine is an independent risk factor for stroke and is frequently and bidirectionally comorbid with epilepsy and depression, pointing at shared underlying pathogenic mechanisms. Treatment of migraine is fully satisfactory in less than one third of patients, calling for better acute and prophylactic medications. The overall mission of the multidisciplinary Leiden Migraine Programme is to identifying prophylactic drug targets specifically for the prevention of migraine attacks.

In the presentation, I shall focus on the emerging genetic, molecular, neurobiological, electrophysiological and pharmacological evidence that rare monogenic and possibly also common multifactorial types of migraine may be “cerebral ionopathies”, leading to enhanced susceptibility for cortical and subcortical spreading depolarisations that may trigger migraine attacks and may also be responsible for the increased risk of stroke in migraine.

Important initial breakthroughs were the identification of gene variants for several rare Monogenic Migraine Syndromes in which typical migraine attacks are part of a wider neurological and non-neurological phenotypic spectrum. These include: (i) Familial Hemiplegic Migraine (FHM), in which migraine attacks are associated with transient (stroke-like) hemiparesis, which is genetically heterogeneous with mutations in the *CACNA1A* neuronal calcium channel (FHM1) gene, the *ATP1A2* glial cell Na^+/K^+ pump ATPase (FHM2) gene, and the interneuronal Na^+ channel *SCN1A* (FHM3) gene that was known to cause a number of severe forms of epilepsy at young age;. (ii) CADASIL, a neurovascular syndrome that is characterised by recurrent subcortical infarcts and dementia and is caused by mutations in the *Notch3* gene; and (iii) Retinal Vasculopathy and Cerebral Leucodystrophy (RVCL), which usually presents with progressive vascular retinopathy and blindness in combination with often dramatic focal and global brain dysfunction and is caused by specific mutations in the *TREX1* gene.

In a subsequent series of functional analysis studies in transgenic migraine mouse models carrying human pathogenic migraine gene mutations, it was shown that above migraine gene mutations all lead to enhanced glutamatergic neurotransmission resulting in a reduced triggering threshold for and increased responsiveness of spreading depolarisations.

Very recent genome wide association studies in several thousand of patients and controls identified a number of gene variants for the common polygenic multifactorial forms of migraine, which all seem to confirm the pivotal role of cerebral hyperexcitability enhancing the susceptibility to spreading depolarisations of the migraine brain.

Selective inhibition of brain hyperexcitability and spreading depression may be a promising novel approach to prevent debilitating migraine attacks.