Migraine biochemistry and visual snow

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Addendum

Summary

The research in this thesis is divided into two parts. **Part I** consists of biochemical studies in migraine, a paroxysmal brain disorder where visual disturbances may form a part of the migraine attack. **Part II** describes the clinical relation between migraine and visual snow, a brain disorder with continuous visual disturbances and that is possibly associated with migraine.

Part I focuses on migraine, a common brain disorder that is characterized by severe headache attacks accompanied by nausea, vomiting, photophobia, and/or phonophobia (migraine without aura). The headache can be preceded by an aura, most often with visual symptomatology, in one-third of patients and these attacks are classified as migraine with aura. Much progress has been made with unravelling the underlying pathophysiological mechanisms of migraine, foremost the identification of cortical spreading depolarization as the probable cause of the aura and activation of the trigeminovascular system as the likely mechanism responsible for generating the migrainous headache. Still, it remains largely unknown how attacks are initiated. The **aim of part I** is to discover biochemical alterations and related disturbed pathways in migraine as they may provide clues why and how attacks develop. Our studies focused on patients outside attacks (interictally), foremost in cerebrospinal fluid (CSF), as this body fluid is in closer proximity to the brain than, for instance, blood. For our analyses, we primarily targeted neurotransmitters and their metabolites, since cortical hyperexcitability is thought to play an important role in migraine and the molecules under investigation may be involved.

In **Chapter 2** we searched the literature on previous biochemical measurements in CSF and blood of migraine patients and investigated whether reported differences, either interictally or ictally, were consistent. Our systematic literature review revealed that 62 biochemical compounds had been measured previously in CSF, across 40 studies. Meta-analysis showed increased CSF concentrations of glutamate, CGRP and nerve growth factor in chronic migraine patients (chronic migraine is defined as having at least 15 headache days with at least 8 migraine days per month) and decreased β-endorphin concentrations in both chronic and episodic migraine patients. Meta-analysis of studies reporting blood concentrations (serum or plasma) confirmed the increase in glutamate and CGRP, although these concentrations were only tested in patients with episodic migraine and not in patients with chronic migraine. Unfortunately, a meaningful comparison of findings in migraine subtypes (with/without aura) was not possible, mainly because the original studies made no distinction. Furthermore, the quality of the studies varied greatly, not only with respect to the selection and matching of patients and controls but also with respect to measurement techniques. Also, the studies in

literature (largely) focused on single molecules, thereby limiting the capability to study biochemical pathways in an unbiased manner.

In **Chapter 3** we emphasized the challenge of large-scale CSF studies by studying a major complication of CSF sampling, namely the occurrence of post-dural puncture headache. We investigated the incidence of post-dural puncture headache and whether smaller needles gave less (post-)dural complaints than larger needles. With smaller 22G-atraumatic needles the incidence of post-dural puncture headache was approximately halved, compared to punctures with larger 20G-traumatic and 20G-atraumatic needles. The increase in CSF collection time with the smaller 22G-needle was only minor – an additional 3 to 4 minutes for 10 mL of CSF – with no increase in experienced discomfort. Therefore, we recommend using 22G-atraumatic needles, both for clinical practice and for research purposes.

For **Chapter 4** we investigated amine profiles in CSF and plasma of patients with episodic migraine. We collected interictal samples from 99 patients migraine with aura, 98 patients with migraine without aura and 96 healthy controls matched for sex, age and diurnal influences. Using a validated metabolomics platform, we measured 30 amines. CSF L-Arginine levels were 10.4% lower in migraine with aura and 5.0% lower in migraine without aura compared to controls. No group differences were found for neurotransmitters glutamate, glutamine or GABA or any of the other amines. Global amine profiles in migraine with aura and migraine without aura were similar but both differed from the profile in healthy volunteers; both in CSF and in plasma. This suggests both migraine subtypes share biochemical pathology outside attacks. Pathway analysis pointed toward pathways involving L-arginine metabolism. This study showed that L-arginine may be an important biochemical target in future studies on migraine pathophysiology. The observed decrease in L-arginine may reflect altered nitric oxide signalling in persons with migraine.

Part II focuses on visual snow, a brain disorder that is characterized by the continuous presence of countless, small, tiny dots in the visual field. Patients often describe it as seeing "tv static", referring to the signal of a detuned analogue television. Visual snow may be related to migraine aura since many visual snow patients have a history of migraine with aura. Moreover, in both disorders cortical hyperexcitability seems to be involved. The aim of this part was to describe the suggested clinical relation between visual snow and migraine. If there is a strong clinical relation with migraine, visual snow may teach us more about potentially shared mechanisms of cortical hyperexcitability between the two disorders.

Chapter 5 provides an overview of the visual symptoms that may be related to

migraine, including visual snow. Literature review shows understanding about the pathophysiological mechanisms involved is limited. Furthermore, for several symptoms the association with migraine is weak.

In **Chapter 6** we investigated migraine prevalence in a population of patients with classical visual snow. Comorbid migraine was present in 30/58 (52%) patients, primarily migraine with aura (27/30). The high prevalence of migraine with aura (47%) suggests migraine with aura is more common in visual snow patients than in the general population (~5%). We also studied the effect of preventive medication for migraine aura for treatment of visual snow in a group of patients that visited the Leiden Headache Clinic. Lamotrigine was prescribed most frequently (N = 26) and resulted in partial remission of visual snow in 5/58 (19%) patients, but none of the patients reported complete remission of their symptoms. None of the other prescribed drugs (valproate (N = 7), topiramate (N = 4), acetazolamide (N = 2), flunarizine (N = 1)) led to any remission except in one patient on topiramate who needed to stop treatment because of adverse events. The study showed that migraine is a prevalent comorbidity in visual snow patients, but that preventive migraine medication does not seem very effective in treating visual snow symptomatology.

In **Chapter 7** we studied migraine prevalence in patients with visual snow triggered after illicit drug use defined as 'hallucinogen persisting perception disorder', abbreviated as HPPD. Most HPPD patients (17/24; 71%) in our study, reported that visual snow started after intake of ecstasy. Several other psychedelic drugs were also reported. As control group we included patients with visual snow who had never used illicit drugs. In contrast to our hypothesis, none of the 24 HPPD cases had migraine, whereas 20/37 (54%) of visual snow patients had migraine. The absence of migraine in HPPD suggests that, at least partly, different pathophysiological factors play a role in both disorders. Furthermore, this study illustrates that the symptom of visual snow can occur in a wide variety of persons and that it will be important to have clear study group definitions for future research on visual snow.

Finally, **Chapter 8**, provides a general discussion of this thesis, with considerations for future research on migraine biochemistry and visual snow.