Migraine, the heart and the brain

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Chapter 9

Summary and general discussion

This thesis describes the results of studies on subjects with migraine and controls without migraine within the population based "Cerebral abnormalities in migraine an epidemiological risk analysis II (CAMERA II) study". These studies include longitudinal brain imaging (part I), right-to-left shunt (RLS) investigation (part II), and cognitive and cerebellar function evaluation (part III). Two clinical based studies are also included; 1) to evaluate the transient effects of the acute migraine attack on cognitive function and 2) to investigate an association between non-shunting cardiac abnormalities and migraine aura.

I Migraine and brain imaging

In our population-based cohort that was followed up after 9 years, women with migraine had a higher volume of deep white matter hyperintensities and also more new lesions. This was not related to the presence of aura symptoms. Measures of migraine severity (eg attack frequency or life time attack load) were not related to progression of brain lesions. In men no difference between migraineurs and controls in deep white matter volume nor progression was found. **(Chapter II)** The prevalence of infratentorial hyperintensities was also higher in female migraineurs (both with and without aura) than in controls. Also progression of infratentorial hyperintensities during follow up was more frequent in migraineurs (trend). Again this was not found in men. (**Chapter II**)

White matter hyperintensities are common with age and increase over time. They are likely ischemic in origin, probably caused by chronic hypo-perfusion at borderzones of vessels and arteriolosclerosis. [1;2] Recently, it was shown that, like in the acute state of ischemia, a border zone with decreased cerebral blood flow, the so called penumbra, surrounds white matter hyperintensities in general, also suggesting an ischemic origin.[3] In our study, female migraineurs were found to have more progression of supratentorial deep white matter lesions and infra-tentorial hyperintensities, not specific for a migraine subtype. These findings somewhat differ from those in a meta-analysis of six population-based and 13 clinical-based studies, in which an increased risk was only present in migraine with aura, and not as in our study in both migraine with and without aura.[4] However studies included in this meta-analysis were heterogeneous, and often did not distinguish between deep and peri-ventricular white matter lesions which is important as their origin is hypothesized to be quite

different. Only one other population based study also reported longitudinal data like our study. The Atherosclerosis Risk in Communities cohort (ARIC) study cross-sectionally found an association between migraine and white matter hyperintensities which was in line with our finding, but they did not find differences in progression over time.[5] Furthermore they did not find a gender effect in this association. Possibly these differences can be explained by the fact that the ARIC study, like most studies in the previous mentioned meta-analysis, did not distinguish between deep and peri-ventricular white matter lesions. Also the headache assessment was only done at baseline, so some controls might have become migraine patients during follow-up and were not analyzed as such. Recently a cross-sectional study with only female twins with and without migraine also did not find an association between deep white matter hyperintensities and migraine. Subjects with cardiovascular history were excluded in this study, and specificly migraineurs with aura were excluded on this history. Also responder rates in migraine were higher than in controls. Both might have biased findings in this study.[6]

Our study was unique as we had a long follow up of both MRI as well as of clinical and migraine specific variables. In this way we were able to show that progression of white matter hyperintensities was not dependent on persistence migraine activity, but also occurred in migraineurs who stopped having attacks. Likewise, progression of lesions was not dependent on attack frequency or total amount of attacks during life time

We have shown that a migraine attack related mechanism does not explain the association between migraine and deep white matter lesions. Thus which attack unrelated mechanism can explain this association? An underlying factor influencing, and causing, both migraine and lesions may be possible, such as a shared genetic factor. An example of this is the co-occurrence of migraine with aura in one third of patients with CADASIL who develop also white matter lesions and stroke and is caused by mutations in the Notch3 gene. Other possible explanations may be non-genetic factors that are associated with migraine as well as white matter lesions, such as endothelial dysfunction. Furthermore, a reduced resting cerebral flow in the brain in the white matter, as reported to be lower in female migraineurs compared to controls, could also explain the higher prevalence of white matter lesions. [7]

For patients and treating doctors is seems reassuring that the migraine attacks itself does not seem to be causative for the lesions. Therefore, preventative migraine medication is not advocated to prevent white matter hyperintensities in women with migraine.

During the follow up of our cohort, new posterior circulation silent infarcts were found in migraineurs, irrespective of gender or migraine type, in 5% compared to 0% of controls. This again was not associated with persistent migraine activity, nor with migraine frequency or life time migraine attack load. (**Chapter II**)

One of the questions that remained after CAMERA-I was: "What is the actual pathological substrate of the so called infarct like lesions, which are found more in the cerebellum of migraine patients"? [8] A recent human combined ex vivo MRI and histopathological study on 40 cerebellar specimens demonstrated that deep cavities in the cerebellum with "infarct-like" appearance on MRI, similar as those identified in our migraine study MRI scans, were indeed true infarcts. The observation of migrainous stroke occurring during a migraine attack would also support the hypothesis of ischemia.[9] Silent infarcts in the cerebellum by definition have not caused any noticeable clinical symptoms, however these silent infarcts were associated with an increased risk of clinical stroke in a non-migraine study.[10] A recent meta-analysis[4] of 19 studies showed that silent infarcts were not more common in migraine wit aura than controls (p=0.52). After this meta-analysis the population based Northern Manhattan Study (NOMAS) was published, which was partly inline with our findings, that migraine was associated with silent brain infarction, however location was not predominantly in the cerebellum which was not consistent with our study.[11] The underlying mechanism of the relation we found between silent cerebellar infarcts and migraine (both with and without aura) remains unclear.

Hypotheses raised are essentially the same as for the relation between white matter lesions and migraine. We found that migraineurs with silent cerebellar infarcts had a less favorable cardiovascular risk profile compared to the migraineurs without these infarcts, but the numbers behind this observation are small, thus results must be interpreted carefully. Both hypertension and hypercholesterolemia were overrepresented in the silent infarct group. An underlying (genetic) factor influencing, and causing, both migraine and infarcts may be possible. It also has been shown that migraineurs have endothelial dysfunction[12] and increased aortic stiffness. [13] Recently it was also shown that high sensitivity C-reactive Protein (hs-CRP) and fibrinogen (both biomarkers of hypercoagulability and inflammation) were elevated in persons with migraine compared to controls.(personal communication) These are all systemic findings increasing the cardiovascular risk.

Right-to-left shunts (RLS) which we found to be more prevalent in migraineurs with aura, can only (partially) explain the risk as these are only over-represented in migraineurs with aura. However we did find a trend towards more cerebellar silent infarcts in subjects with RLS (see also part II, the heart and migraine).

II Migraine and the heart

We showed that the prevalence of RLS in migraine with aura was increased compared to controls without migraine and migraineurs without aura. (**Chapter III**) However, the relative risk was not as high as in clinic based studies, probably because in our study the occurrence of RLS was also relative common in the control group. In our study all investigators were blinded for migraine diagnosis, in contrast to the earlier clinic based studies, making our finding more likely to be reliable. A broad range of embolic structures is able to cause migraine attacks, although the occurrence of actual attacks in these specific embolic rich circumstances seems quite low. (**Chapter IV**)

Both the finding of the association between RLS and migraine with aura in the general population, as well as the finding that persistence of migraine activity was associated with the presence of spontaneous RLS, add to the evidence of an association between RLS and migraine, especially in migraine with aura. Several hypotheses have been raised to explain the higher prevalence of RLS in this subtype of migraine. A widely accepted theory is that small emboli from the venous circulation bypassing the pulmonary filter by crossing a right-to-left shunt may induce migraine aura as these emboli reach the cerebral circulation. In this model the RLS enables emboli reaching the brain. **Chapter V** summarizes numerous case-reports of patients developing migraine aura after pathological induced emboli. From animal studies there is accumulating evidence that emboli can indeed induce cortical spreading depression, the underlying pathophysiological substrate of the aura phase. In patients with ischemic stroke these cortical spreading depressions have been recorded with subdural electrocorticography.[15] Another theory is that RLS enables metabolites like serotonin or carbon dioxide from the venous circulation to enter the systemic circulation. Recently, it was shown that migraineurs with RLS have a reduced capacity of effective cerebral vasodilatation, which suggests that mentioned substances from the venous circulation may affect this auto-regulation.[16] The evidence for a link between RLS and migraine aura is quite strong, although the actual role of RLS is probably limited.

Our study (**Chapter III**) was the first to include both migraineurs with persistent migraine activity as well as migraineurs who had ceased having attacks. We showed that persistence of activity was related to the presence of spontaneous RLS.

This is in line with the theory in which RLS enables passage of emboli. However it is evident that the presence of RLS not fully explains the occurrence migraine aura, as not all migraineurs with aura have a RLS, and migraineurs without aura also (but in a lower percentage) have RLS and never experience an aura. Well designed randomized, sham-controlled, RLS closure studies are needed to prove if this association is causal.

RLS was not associated with subclinical cerebellar infarcts, although there was a trend for this association in the posterior circulation. (**Chapter III**)

Several studies provided evidence that RLS (specific patent foramen ovale) is associated with clinical (crypotogenic) stroke. Well known risk factors for ischemic (silent) stroke are hypertension, smoking, diabetes and atrial fibrillation.[17] The additional risk of an RLS probably is relatively small. Due to limited number of cerebellar infarcts, adjustments for all major riskfactors on methodological grounds unfortunately in our study was not possible. Except for some studies [18;19] showing that cardiac emboli favor the posterior cerebral circulation, there are no good explanations why RLS subjects in our study showed a trend for more cerebellar silent infarcts. In a migraine patient who suffers a (silent) stroke in the posterior circulation and who does not have additional cardio-vascular risk factors, screening for RLS seems a reasonable advice.

We also showed that aortic root replacement in a heterogeneous group of cardiac patients was associated specific with migraine with aura. (**Chapter V**)

We were the first to show that the increased migraine (in particular with aura) prevalence among Marfan patients was specifically found in the group who underwent aortic root replacement. Several other large vessel diseases have been associated with migraine. For example being a migraineur doubled the risk of carotid artery dissection [20] and subjects with angiographically confirmed carotid artery dissection have been described with attacks of transient symptoms exactly resembling migraine wit aura. Recently a genetic study on carotid dissection and a study on migraine both identified the same variant on chromosome 6 (PHACTR1 gene), reducing the risk of carotid dissection as well as the risk of migraine with aura.[21-22] Interestingly wide aortic root diameter also is a risk factor of carotid dissection,[23-24]

and widening of the aortic root in Marfan patients was the main reason to perform aortic root replacement. An underlying large artery arteriopathy is evident in Marfan and believed in carotid dissection. Also in reversible vasoconstriction syndrome (RCVS), migraine is considered a risk factor. And some patients both have RCVS and carotid dissection, and 60% of these subjects were migraineurs.[25] All these findings point towards a role of abnormal large vessel dilatation (or altered cerebrovascular tone) in migraine, although the mechanisms and possible causative link remain to be proved.

The Delphi approach was used to define recommendations from cardiologists specialized in rhythm disorders for safe use and EKG monitoring of high dose of verapamil. These experts agreed on performing a pretreatment EKG in patients using verapamil for the first time. Pretreatment EKG was deemed not necessary in subjects who did not have cardiac adverse events during a previous period of verapamil use. No consensus was reached on EKG monitoring during verapamil treatment and dose adjustments. Consensus about absolute and relative contra-indications for continuing high dose verapamil largely followed FDA recommendations.No consensus-based recommendations on EKG monitoring during verapamil treatment and around dose increases can be given although, based on the literature EKG prior and after every dose increase would be our recommendation. Individual patient characteristics always have to be taken into account.
(**Chapter VI**)

III Migraine and brain function

We did not find any impaired interictal (in between attacks) cognitive function in migraine using a large battery of neuropsychological tests covering function of supratentorial brain structures. (**Chapter II**). We did show that a high white matter lesion load was probably (trend) associated with impairment of memory. This again did not differ between migraineurs and controls. (**Chapter II, etable 3**) In our study evaluating cognitive function shortly after a migraine attack, we found interictal differences unrelated to the previous attack. Migraineurs showed impairment in the processing of global visual features compared with controls. (**Chapter VIII**)
Some studies reported inter-ictal cognitive deficits in migraineurs, while other reported no differences between migraine and controls.[26-30] The previously found

differences represented different domains like psychomotor speed, executive function, language, attention, memory and visual processing. In our CAMERA-II study no difference were found between groups on memory, concentration, attention, executive function, psychomotor, processing speed, organization, fluid intelligence and visuospatial skills. Our study had the strength that it was large and investigators were blinded. The absence of impairment among migraineurs (and even a better global cognition) was recently shown in a large population study, results which were (partly) in line with our study.[31]

We were able to show (trend) that deep white matter lesions were associated with impaired memory function. This is in line with previous studies[32] and underlines the sensitivity of used cognitive battery, as the amount of white matter lesions compared to non-migraine studies was limited.

If the impaired cognitive functions among migraineurs in these clinical based studies were the result of repeated migraine attacks, we hypothesized that impairment is more pronounced shortly after an attack. Therefore we studied cognitive function shortly after a migraine attack. (**Chapter VIII**). However no evidence for temporary changes in cognitive function could be found in the post-ictal state.

Our study design was unique as migraineurs were studied after the migraine attack, they had to be pain free. This allowed us to rule out any negative effect on cognitive function caused by pain itself. This however on the other hand led to an average of 17 hours following the end of the attack before testing. The use of controls was a strength of our study, in that way we were able to eliminate the effect of a learning effect.
We did however find that migraineurs did not show the global precedence effect (perceiving the global letter, which was built from a number of so called local letters first and faster) which was present in controls. In other words migraineurs were impaired in seeing the wood for the trees. This may point towards dysfunction of higher visual cortical areas or connectivity between areas involved in visual processing. Our finding is in line with a study that migraineurs have higher thresholds for the recognition of global shapes.[33]

Contrary to smaller studies, we could not demonstrate an impaired inter-ictal function of the cerebellum in (non-hemiplegic) migraine subjects, using several measurements sensitive for dysfunction of several cerebellar anatomic regions. Migraineurs did not differ from non-migraine controls for fine motor speed

and coordination, perceptual intelligence and motor function, cerebellar motor coordination and learning of limb movements, associative cerebellar motor learning and vestibular motor coordination.(**Chapter VII**).

Our study was the first to assess a broad range of cerebellar functions in a population based study and with investigators blinded for migraine/ control status. We failed to find any evidence of impaired cerebellar function using an array of tests covering the functions of the main parts of the cerebellum. Previous studies which suggested subclinical cerebellar dysfunction were all small clinical based and unblinded.[34-38] Our test battery consisted of highly sensitive clinical tests, which was shown by the fact that they did show deficits in a relatively small group of FHM patients which were tested with the same test protocol. Thus, in contrast to previous findings, our findings argue against the hypothesis that cerebellar function is subclinically impaired in migraine patients. Also in general these cerebellar infarcts did not cause any functional impairment.

Future perspectives

We showed that both subclinical cerebellar infarcts as well as deep white matter hyperintensities in migraine patients occur irrespective of current migraine activity or past and present attack load. Most likely an underlying factor, for instance endothelial dysfunction or a shared genetic factor may be the causal link in this association. The role of comorbid RLS on ischemic lesions seems small, if any. Future studies should focus on identifying the underlying mechanism between migraine and white matter lesions in women.

The association between RLS and migraine with aura, which we now demonstrated in the general population, adds to the evidence that emboli can be able to induce cortical spreading depression which is the underlying mechanism for the migraine aura. However, as evidence for a prophylactic effect of RLS closure is currently still lacking, we advice against screening for RLS in migraine with aura patients.

Although migraine is associated with subclinical structural brain changes, this seems unrelated to attack load and these lesions do not cause functional impairment. Also does migraine (by any other mechanism) not lead to impairment of brainfunction. Future studies should focus on identifying the underlying mechanism between migraine and white matter lesions specific in women.

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