Diagnostics in patients presenting to the emergency room with headache

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Appendix

ENGLISH SUMMARY

NEDERLANDSE SAMENVATTING

DANKWOORD

CURRICULUM VITAE

LIJST VAN PUBLICATIES

ENGLISH SUMMARY

Headache is a common problem and a frequent reason for presentation at the emergency department. For the treating physician the challenge lies in separating the innocent, albeit painful, primary headaches (migraine, cluster headache, tension type headache) from the secondary headaches with high morbidity and mortality such as subarachnoid hemorrhage, cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, cervical arterial dissection or meningitis.

This thesis focuses on a variety of diagnostic tests, which are used to identify these different types of headache. The aim is not only to evaluate the diagnostic yield of these tests, but also when to apply them in which patients. A large part of this thesis is dedicated to the diagnostic yield of CTA in patients presenting to the emergency department with headache. In patients with acute headache and a normal non-contrast cerebral CT (NCCT) we found a higher number of abnormalities than may be expected in the general population. In our first study on this subject we found 13 (19%) vascular abnormalities in 70 patients (Chapter 2). In this group a considerable number of patients had previous neuro-vascular episodes such as a SAH or CVT. Furthermore, these patients were included based on a lumbar puncture without signs of hemorrhage. This was in the period before a groundbreaking study proved from Canada that if a NCCT is performed within 6 hours after the start of headache, a lumbar puncture is no longer needed to exclude SAH. This means that a selection bias may exist for these patients as a lumbar puncture is considered to be pain- and stressful and would only have been performed in patients with definite acute headache.

In our follow-up study (Chapter 3) we combined a more recent population of patients with acute headache who received a CTA in a series from the LUMC and Haaglanden MC with those described in literature in a meta-analysis and found a vascular abnormality in 7% of patients. Most of these abnormalities consisted of aneurysms of which the clinical relevance could not be clarified. In the general population an aneurysm can be found in 2-3%, in this group we found a prevalence of 5.4% aneurysms. We could not elucidate how many of these aneurysms had bled or not. Therefore we could not determine which percentage of aneurysms was causative of the acute headache and how many were incidental findings, i.e. unruptured intracranial aneurysms. In a small number of patients we found a definite clinically relevant abnormality such as cerebral venous thrombosis (three cases; 0.5%), revisable cerebral vasoconstriction syndrome (four cases; 0.5%), Moya moya (two cases; 0.3%), cervical arterial dissection (two cases; 0.3%) and ischemia (one case; 0.1%). The number of patients needed to scan to find one abnormality was 14 and the number needed to scan to find a definite clinically relevant abnormality was 61. Thus it seems that the number of clinically relevant findings on CTA in patients with acute headache, a normal neurological examination and normal NCCT is low. This correlates with findings of earlier follow up studies that showed that morbidity in this group is low. However, the clinically relevant abnormalities did warrant medication change and intensified follow-up. Therefore it

seems unwise to definitely advise against CTA altogether, but the purposeful use of CTA does become important. If it were possible to identify patients for CTA with a high diagnostic yield we could minimize the number of scans but still identify patients that need additional treatment. Therefore, we proceeded to construct a prediction model for identifying vascular abnormalities with CTA in patient with acute headache.

We found, unsurprisingly, that an abnormality in NCCT is the strongest predictor for identifying an abnormality on CTA (Chapter 4). Other factors that contributed significantly to finding an abnormality were ongoing lowered consciousness and abnormalities at neurological examination. But the combination of these factors gave no better diagnostic characteristic than an abnormal NCCT alone. These findings are somewhat of an open door in clinical practice as any of these clinical findings would prompt follow-up imaging in any case. We were most interested in patients with normal NCCT as in this group the decision whether or not to perform additional imaging is less clear. We found a very small number of clinically relevant vascular abnormalities that warranted treatment. We could not identify clinical factors for the performance of CTA. A prospective study to identify selection criteria for CTA in patients with acute headache, normal neurological examination and normal NCCT is now being performed.

In some cases testing of cerebrospinal fluid for hemorrhage is still necessary. We compared two workflows for evaluating bilirubin, a blood breakdown product that is found in patients after subarachnoid hemorrhage, in cerebrospinal fluid (chapter 5).

The Leiden method is a calculation model used in combination with photospectometry testing of CSF and is 100% sensitive. In photospectometry the wavelength of various blood breakdown products is used to determine their presence in cerebrospinal fluid. Specificity of the Leiden method is lowered if the cerebrospinal fluid contains a lot of protein or if patients have high serum bilirubin. The specificity can be increased if the UK NEQAS method is applied on the cerebrospinal fluid samples that test positive with the Leiden method. This requires additional evaluating using a decision tree by the local clinical chemist. This workflow assures both highest specificity and highest laboratory workforce efficiency.

Sometimes it may be possible to avoid additional imaging. In patients suspected of CVT additional CT venography (CTV) or MRI is often performed to evaluate this possibly fatal condition. D-dimer is a protein involved in the thrombotic chain and is often determined in patients suspected of pulmonary embolism (PE) or deep venous thrombosis (DVT). In patients with a low risk of PE or DVT based on clinical criteria and with a normal D-dimer do not need additional imaging e to the very low risk of thrombosis. In this thesis a meta-analysis was performed to evaluate whether CTV may be avoided in patients with a low risk of CVT (isolated headache) and a normal D-dimer (Chapter 7). In a group of 636 patients we found 45 patients with CVT. Of these 45 patients one had a false negative D-dimer. Sensitivity of D-dimer for detecting CVT in patients with isolated headache was 97.8% (95% CI: 88.2-99.6 %), specificity was 84.9% (95 % CI: 81.8-87.7%), the

positive predictive value was 33.1% (95% CI: 25.2-41.7%) and negative predictive value was 99.8% (95% CI: 98.9-100%). D-dimer can be used to avoid additional imaging in low risk CVT patients.

Finally we studied intrathecal procalcitonin production in patients with a suspicion of bacterial meningitis (chapter 6). Procalcitonin is an acute phase protein which is released in the serum during bacterial infection. In serum it has been proven to discriminate between bacterial and viral infections, or auto-immune responses. In the cerebrospinal fluid (CSF) procalcitonin is also present and most likely produced by glia cells. In our study we showed that procalcitonin is significantly raised in patients with bacterial meningitis in comparison with patients with viral meningitis or acute headache. Furthermore, in patients after neurosurgical intervention procalcitonin is relatively more raised in CSF than in serum. This skewed distribution seems to indicate a direct port of entry rather than a raised value due to for instance a traumatic puncture. All in all procalcitonin seems a promising diagnostic marker in suspected meningitis.

We have started several follow-up studies concerning the subjects discussed here. A prospective multi-center study is ongoing to evaluate the diagnostic yield of CTA in patients with acute headache, normal neurological examination and a normal NCCT. Also a follow-up study on the recurrence rate of episodes of acute headache has been started.

Finally a clinical study evaluating the day to day of procalcitonin in cerebrospinal fluid in patients with an external ventricular drain is being performed.