Diagnostics in patients presenting to the emergency room with headache

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Chapter 8

GENERAL DISCUSSION

In this thesis several diagnostic tests have been evaluated ranging from CSF testing to neuro-imaging to D-dimer testing in serum in patients who present to the emergency room with headache.

NON CONTRAST CT AND CT-ANGIOGRAPHY

Whether or not to perform additional imaging in patients with acute headache has been under much debate. The main arguments against performing a CTA have been based on follow-up studies combined in a pooled analysis, which showed that morbidity after excluding SAH (either with NCCT < 6h or an LP without signs of hemorrhage) was very low [1]. However follow-up in the included studies was limited and did not focus on CVT, (viral) meningitis, arterial dissections or RCVS. In fact, none of these conditions was diagnosed. A surprising finding, which seems highly unlikely considering the expected prevalence of these conditions in this population.

CVT may present with acute severe headache, without neurological deficit in 3-13% of cases [2,3]. Cervical arterial dissection has been reported to present with acute headache as the only symptom in 20% of cases [4,5]. RCVS has been reported to present with isolated headache in 57% to 88% of cases [6].

In our study addressing bilirubin detection (chapter 5) we found a surprisingly large number of patients with a vascular abnormality on CTA with a normal neurological examination and normal NCCT (19%). A comparable study found 6.6% vascular abnormalities in a group of patients with acute headache, normal neurological examination and normal NCCT [7]. The number of detected abnormalities in both studies was higher than might be expected in the general population, but the variation between two percentages was high. This inspired us to perform further studies to determine whether after a normal NCCT the search for a cause of acute headache is really over.

We found a lower percentage of vascular abnormalities in our meta-analysis in patients with acute headache, a normal neurological examination and normal NCCT of 7.4%. In this study we attempted to improve generalizability by combining a retrospective group from the Leiden University Medical Center and Haaglanden MC with patients from literature. The majority of abnormalities consisted of aneurysms. It is unclear whether these aneurysms had ruptured or were incidental findings without clinical relevance. Not all patients received lumbar punctures and therefore we could not determine if the aneurysms had bled. If an aneurysm has not bled the need for treatment is determined by its location and size and patient related factors such as age and hypertension [8]. In some case reports inflammation of an aneurysm or sudden distension has been named as a possible cause of acute headache [9-12]. Generally it seems more likely that unruptured intracranial aneurysms (UIA) are not the cause of acute headache but must be deemed a co-incidental finding. In our first retrospective study we found eight aneurysms, all unruptured since the LP did not show any signs of hemorrhage. Of these eight

aneurysms six were either coiled or clipped. The reason for this was not always clear, but four were large, with a size of or over 7 mm. As other aneurysms were left untreated they may give rise to much fear and insecurity in the patient. The need for medical follow-up and radiation due to excess scanning imposes an additional burden. The finding of the aneurysm may have lowered the quality of life of these patients.

Finally we also found abnormalities that were definitely clinically relevant. These consisted of diagnoses such as CVT, RCVS and arterial dissections. However the number of definitely clinically relevant abnormalities was only 1.6%. How to detect those, but avoid making unnecessary CTA's?

In chapter 4 we attempted to construct a prediction model to determine clinically relevant findings on CTA in patients with acute severe headache. We found that the presence of an abnormal NCCT is the strongest predictor for finding an abnormality on CTA. When other significantly predicting factors such as ongoing lowered consciousness and subjective neurological deficits were included in a combination prediction model, it did not significantly increase the AUC. For clinical practice this seems an open door, as an abnormality on NCCT will directly warrant additional imaging either in the form of CTA or MRI/MRA, but it is disappointing that other patient characteristics did not have additional predictive value.

We were more interested in clinical factors predicting abnormalities in patients with a normal NCCT. In this group the decision to perform additional imaging is more challenging and evidence when to perform a CTA or MRI is unavailable. Diagnostic yield in this group was low however (3.6%). In fact the yield was so low that isolated clinical predictors in patients with a normal NCCT could not be determined.

The variation in the prevalence of abnormalities we found in our studies is striking and may be due to several potential biases. In the group with 19% abnormalities (acute headache, normal neurological examination, normal NCCT and normal LP) all patients received a lumbar puncture without signs of hemorrhage. The patients were included retrospectively from a time when protocol mandated a lumbar puncture for all patients with acute headache even if non-contrast CT was normal within 6 hours of presentation. The lumbar puncture is considered to be pain- and stressful for patients as well as time consuming. Due to these restraining factors the selection of patients may have been stricter with exclusion of cases with doubtful headache onset or clinical symptoms. Also, as this was a retrospective study there may have been an indication bias for performing the CTA. The patients in this series also had a high recurrence rate of vascular abnormalities raising the number of abnormalities. It seems likely that these patient related factors such as previous SAH or CVT were selection factors to perform a CTA.

All in all the high prevalence of 19% vascular findings found in the first, retrospective study, could not be reproduced in our cohort studies that followed and so, also in relation to literature, seems an unlikely high number. It seems more likely that the number of clinically relevant

abnormalities is around the 1.6-1.8%, which we found in our meta-analysis and prediction model [13,14]. Although few, the severity of the detected abnormalities makes it hard to advise against CTA in this group. Currently a prospective study in patients with acute headache, normal neurological examination and normal NCCT is ongoing with the aim to determine a more precise estimate of the prevalence of abnormalities in this group and potential patient factors related to the finding of a vascular cause for the acute headache. Thus, we hope to be able to find a way to purposefully apply the CTA with a high yield of diagnoses or be able to prove that it can be foregone altogether and reduce diagnostic burden and costs.

Cerebral spinal fluid

Bilirubin

In chapter 5 we evaluated two methods of photospectometry for the determination of bilirubin in cerebrospinal fluid (CSF) in patients with acute severe headache. Photospectometry is, surprisingly, not yet ubiquitous as a determination method for bilirubin in CSF. In the United States visual inspection is still widely used with a sensitivity of only 47.3% [15].

The determination of bilirubin remains important in patients who present more than six hours after their acute headache. These patients require CSF testing to exclude SAH. Furthermore, if an aneurysm is found it is important to determine whether it is a ruptured aneurysm, because this is an important factor which determines the need for treatment. We compared the UK NEQAS method with the Leiden method in 391 patients. The Leiden method is a calculation model which evaluates the presence of blood pigments at set absorption values and thus calculates the concentrations of bilirubin, methemoglobin and oxyhemoglobin. The UK NEQAS ads a decision tree after photospectometry. In both methods the sensitivity for identifying an aneurysm after a positive test result was 100%. However, with the Leiden method specificity was lower. Confounders in the Leiden method were viral and bacterial meningitis and cerebral venous thrombosis. The UK NEQAS has a more conservative cut-off value also resulting in more negative results. This did not affect sensitivity. The down side of the UK NEQAS method is that it requires additional evaluation from either an experienced laboratory technician or clinical chemist. We advise the use of the UK NEQAS method only on CSF results suspected of SAH with the Leiden method in order to optimize work flow.

Procalcitonin

In chapter 6 we described a prospective study, which evaluated the production of intrathecal procalcitonin in patients suspected of bacterial and viral meningitis. Two previous studies showed significantly higher PCT concentrations in CSF in patients with bacterial meningitis compared with tick-borne encephalitis or viral meningitis [16,17]. We included a varied population of patients with both community acquired bacterial meningitis and bacterial meningitis after neurosurgical intervention. We found that procalcitonin in CSF was significantly raised in patients with bacterial meningitis compared with patients without bacterial or viral meningitis. In patients after neurosurgical intervention the PCT in CSF was raised relatively more than in plasma suggesting a direct

port of entry of infection. Particularly after surgery the spillage of plasma in CSF may give rise to confusing findings in conventional CSF chemistry. Even when corrected for erythrocyte numbers the PCT CSF:plasma ratio was still higher in patients with post neurosurgical bacterial meningitis.

A limitation of this study was its limited size. Second, we could not prove all bacterial meningitis cases with a positive culture. To improve the specificity we applied specific CSF chemistry criteria for the diagnosis of bacterial and viral meningitis.

Despite the small number of patients we feel PCT may be of interest as a valuable diagnostic marker to differentiate bacterial meningitis from aseptic meningitis, particularly in patients who had a neurosurgical intervention.

D-dimer in serum

In chapter 7 we presented a meta-analysis evaluating the diagnostic characteristics of D-dimers in patients, which were suspected of cerebral venous thrombosis (CVT) with a normal neurological examination and normal non-contrast head CT. In these low risk patients a normal D-dimer may aid the decision whether CT venography is necessary or not. There are conflicting and limited data on patients with isolated headache. One often cited study found negative D-dimers in 5 out of 19 (26%) patients with CVT and isolated headache [18]. Another, prospective, study found no false negative D-dimers in 20 patients with isolated headache [19].

In our study, we found D-dimers have a high negative predictive value in patients with isolated headache for excluding CVT of 99.8%. Sensitivity is lower but comparable to the values accepted in PE and DVT. Low risk patients were defined as headache patients with a normal neurological examination, normal standard head CT and absence of risk factors such as pregnancy or puerperium. Normal D-dimers in these patients may reduce unnecessary imaging, making it a potential valuable marker. In patients with additional risk factors such as pregnancy or the use of oral anti-contraceptives additional imaging is still necessary and Ddimer is insufficient to exclude CVT.

Our study had some limitations. First, patients were included retrospectively. Second, varying methods of D-dimer determination made it impossible to determine a D-dimer cut-off value or diagnostic area under the curve. Furthermore, due to missing data on control patients with isolated headache we could not calculate negative and positive predictive values for the entire available population. However, our meta-analysis is the only one focusing on such a large group of patients with isolated headache suspected of CVT. The population is multi-centered and international, improving generalizability.

FINAL CONCLUSIONS

In patients with acute headache who present to the emergency room the yield of a CTA is highest in patients with an abnormality on head NCCT. The yield in patients with normal NCCT is low. A multivariable prediction model showed that clinical symptoms have no added value over the variable 'normal NCCT' alone. In patients with acute headache and a normal NCCT the yield of CTA is higher than in the general population, but findings consist mainly of unruptured intracranial aneurysms that do not always have treatment implications and may generate anxiety. The sporadically found cervical dissection, CVT or RCVS may justify performing CTA. At the moment there are no clinical factors, which can predict which patients will have an abnormality on CTA after a normal NCCT.

In patients who are suspected of CVT but who have no additional risk factors besides headache, CT venography is unnecessary if the D-dimer level in serum is normal. The negative predictive value of D-dimer in this group is very high for excluding CVT.

If CSF testing for the presence of bilirubin is required, the Leiden method, an iterative calculation model, is 100% sensitive. Specificity can be increased if the UK NEQAS method is applied on the CSF's that test positive with the Leiden method. This workflow assures both highest specificity and highest laboratory workforce efficiency.

In patients suspected of bacterial meningitis procalcitonin determination in CSF may become a valuable marker particularly in patients with confounding factors such as recent neurosurgical intervention. The differentiation from aseptic or septic meningitis in this group is difficult and an additional marker would be valuable to avoid unnecessary antibiotic treatment.

FUTURE PERSPECTIVES

Whether a CTA/CTV is needed in all patients with sudden severe headache is still unknown. A prospective study is needed to evaluate which patients need to be selected for CTA/CTV or whether it can be foregone altogether. We recently started a prospective study performing CTA in all patients with acute headache, normal neurological examination and normal non-contrast head CT. This study is carried out in a multi-center setting in the Haaglanden MC and Leiden University Medical Center. We hope to ascertain the yield of CTA in this patient group and possibly define patient characteristics that may aid in the decision whether or not to perform a CTA.

The prognosis of patients who presented the emergency room with acute headache in terms of long-term diagnosis, recurrent episodes of headache and quality of life is unknown. A follow-up study evaluating this is being started in the MCH and the LUMC. We aim to contact patients who presented in the past 4 years with acute headache to our emergency departments and will

perform a standardized questionnaire concerning possible new episodes of acute headache and long-term diagnosis. A secondary outcome measure will be how the patient experienced the initial emergency room visit; was the final diagnosis clear? Were they sufficiently put at ease? Did they receive expected tests?

A further prospective study is needed to evaluate the sensitivity and specificity of D-Dimer in patients suspected of CVT. However, this is a challenging study since CVT needs to be sufficiently excluded in order to be able to make conclusions.

Finally, more research on the use and sensitivity of determining procalcitonin in CSF is needed to evaluate the role of procalcitonin as a biomarker for bacterial meningitis. Particularly the dynamics of procalcitonin levels during the presence of an external ventricular drain (EVD) is of interest. A prospective study is being set up in our center in which daily determination of PCT will be performed in patients with an EVD in relation to daily CSF cultures to further assess diagnostic sensitivity and specificity.

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