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Diagnostics in patients presenting to the emergency room with headache

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DIAGNOSTICS IN PATIENTS PRESENTING TO THE EMERGENCY ROOM WITH HEADACHE

I.M.E. ALONS

Colofon

Diagnostics in patients presenting to the emergency room with headache

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DIAGNOSTICS IN PATIENTS PRESENTING TO THE EMERGENCY ROOM WITH HEADACHE

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CONTENTS

Chapter 1

INTRODUCTION

Headache in general is a common problem and accounts for up to 4.5% of the visits to the emergency department [1]. For the treating physician the challenge lies in differentiating patients with primary headaches, such as migraine, tension type headache, or cluster headache, from patients with possible life threatening secondary headache. The causes of secondary headaches can be divided into three main groups: vascular causes, infectious and trauma. A suspicion of secondary headache may arise in patients who present with first ever headache, in acute or worst ever headache, in the presence of neurological deficit on examination or in patients with fever, systemic illness, pregnancy or immune deficiency.

Acute headache is defined as a severe headache that peaks within five minutes [2]. A subarachnoid hemorrhage (SAH) is the cause of isolated acute headache in approximately 11-25% of patients [3,4]. This is a diagnosis should not be missed as SAH has a high mortality and morbidity [4-7]. Other secondary headaches of vascular origin may be suspected in acute headache. Reversible cerebral vasoconstriction syndrome (RCVS) may be a cause of 'benign' thunderclap headache in which non-contrast head CT and LP are normal. It has been reported to be present in one out of eleven (8.8%) of patients with acute headache in whom signs of SAH are absent [8]. While some cases occur spontaneously or in the post-partum period, the majority of cases (60%) is caused by vaso-active substances (nasal decongestants, cannabis or XTC). It may have a benign course, but also ultimately cause SAH, cerebral hemorrhage or ischemia. Diagnosis can be made with angiography or MR angiography but imaging needs to be repeated over time [9]. Sometimes headache is the only symptom of vascular disease. Cervical artery dissection (CAD) may present with acute headache alone in 8% of cases[10,11], cerebral venous thrombosis (CVT) present with isolated headache in one in seven patients (14%) [12,13]. Cerebral ischemia may present with isolated headache in 2 to 25% of patient cases [14].

These causes of headache may still be present when neurological examination is normal. Herein lies a challenge: selecting the patients who benefit from CT angiography (CTA). In the current medical practice there is more focus on diagnostic sensitivity than specificity and the danger of too many diagnostic procedures is increasingly present, fuelled by the fear of missing an important diagnosis.

Another challenge is the selection of the correct imaging modality. In patients with a clear neurological deficit or altered consciousness after headache, either acute or not, it is clear that at least a non-contrast head CT or MRI should be performed. The imaging of the cervical and intracranial arteries with CT angiography (CTA) or MR angiography (MRA) may give additional information on the presence of RCVS, dissection or CVT. However, the choice for either CTA or MRI/MRA is also determined by the availability of each imaging modality and cost and duration of the scan. In the emergency department setting the high pressure on resources and time make MRI/MRA a less attractive imaging option. However the diagnostic yield of CTA may be insufficient. Furthermore, a CTA causes added radiation exposure and iodine contrast may cause allergic reactions and nephropathy.

What could be the consequence of a missed diagnosis in patients with acute headache? A pooled analysis of follow up studies with normal neurological examination and normal CT found no SAH after six months to one year follow up [15]. The authors advocated that no additional imaging is necessary. Unfortunately follow up time was relatively short and not all patients received additional CTA or MRI. The authors suggest that the natural course in these patients is benign even if other diagnoses such as RCVS, dissections, CVT or meningitis are missed.

Patients presenting to the emergency room may have a wide range of secondary headaches or non-threatening, albeit painful, primary headache. In this thesis a variety of diagnostic tests and their diagnostic yield are evaluated in patients with both vascular and infectious secondary headache. In each case the question is addressed whether expansion or reduction of diagnostic testing is necessary. Apart from identifying patients who benefit from cranial imaging we also searched for methods to avoid unnecessary scanning. We evaluated the yield of CTA in patients with acute headache in a retrospective study and a meta-analysis in **chapter 2 and 3**. Secondly we evaluated possible clinical criteria for a more purposeful selection of headache patients for CTA in **chapter 4.**

In the past few years lumbar puncture after acute headache is performed less frequently. The turning point has been the publication of an article which showed that when a CT is made within 6 hours after the start of the acute headache a lumbar puncture is no longer necessary to rule out SAH due to high sensitivity of current CT techniques [16]. If CT is performed more than six hours after acute headache a lumbar puncture is still mandatory to exclude hemorrhage. If other diagnoses necessitating cerebrospinal fluid testing are suspected a lumbar puncture is of course also needed. Also, if on imaging an aneurysm is detected a lumbar puncture is still necessary to evaluate whether this aneurysm has bled or whether it is an unruptured intracranial aneurysm (UIA) and a coincidental finding. The lumbar puncture is needed to evaluate intrathecal bilirubin, a blood breakdown product. Visual inspection lacks sensitivity and photospectometry is used to determine bilirubin based on an absorbance of 450-460 nm. We compared two methods of photospectometry evaluation in order to evaluate sensitivity and specificity in **chapter 5**.

To further investigate the value of cerebrospinal fluid (CSF) analysis we also performed a prospective study concerning the determination of procalcitonin in CSF in the diagnosis of bacterial meningitis. Viral or bacterial meningitis may present with headache alone and may be difficult to differentiate based on classic CSF findings [17]. Patients with an external ventricular drain after SAH have an increased risk of contracting bacterial meningitis due to a foreign body. Clinical signs and symptoms may be unclear as patients with SAH also may have nuchal rigidity and lowered consciousness. A diagnostic marker to differentiate between bacterial infection and aseptic meningitis would be valuable.

Procalcitonin is an acute phase protein and may become such a marker. There is evidence suggesting it is produced intrathecally by glia cells [18]. In serum it is produced in response to

bacterial infection. We studied procalcitonin formation in a varied group of patients suspected of viral or bacterial meningitis in **chapter 6**.

In patients with acute or worst ever headache cerebral venous thrombosis is often considered. Patients with a normal neurological examination may have CVT and are at risk for secondary deterioration [19]. In patients suspected of pulmonary embolism or deep venous thrombosis Wells criteria are employed in combination with D-dimer to determine which patients are at low risk. Patients in the low risk category do not require further imaging. In **chapter 7** we performed a meta-analysis to determine whether D-dimer may play a similar role in the work up of patients with suspected CVT and a normal neurological examination and normal non-contrast head CT.

REFERENCES

1. Torelli P, Campana V, Cervellin G, Manzoni G. Management of primary headaches in adult Emergency Departments: a literature review, the Parma ED experience and a therapy flow chart proposal. Neurol Sci. 2010;31(5):545
2. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm Lancet. 1986 2:1247-1248
3. Landtblom AM, Fridriksson S, Boivie J , Hillman J, Johansson G, Johansson I. Sudden onset headache: a prospective study of features, incidence and causes. Cephalalgia 2002;22:354–360
4. Linn FH, Wijdicks EF, van der Graaf Y, Weerdesteyn-van Vliet FA, Bartelds AI, van Gijn J. Prospective study of sentinel headache in aneurysmal subarachnoid haemorrhage. Lancet. 1994 27;344:590-3.
5. Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache.. J Neurol Neurosurg Psychiatry. 1998 65:791-3.27;344(8922):590-3.
6. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med. 2000 342:29-36
7. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007 27 369:306-18
8. Grooters GS, Sluzewski M, Tijssen CC. How often is thunderclap headache caused by the reversible cerebral vasoconstriction syndrome? Headache. 2014 54:732-5.
9. Ducros A, Bousser MG. Reversible cerebral vasoconstriction syndrome. Pract Neurol. 2009 9:256-67.
10. Arnold M, Cumurciuc R, Stapf C, Favrole P, Berthet K, Bousser MG. Pain as the only symptom of cervical artery dissection. J Neurol Neurosurg Psychiatry. 2006 77:1021-4.
11. Maruyama H, Nagoya H, Kato Y, Deguchi I, Fukuoka T, Ohe Y, Horiuchi Y, Dembo T, Uchino A, Tanahashi N. Spontaneous cervicocephalic arterial dissection with headache and neck pain as the only symptom. J Headache Pain. 2012 13:247-53.
12. de Bruijn SF, Stam J, Kappelle. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet. 1996 348:1623-1625.
13. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal Neurology Neurosurgery Psychiatry 2005 76:1084-1087.
14. Mitsias P, Ramadan NM Headache in ischemic cerebrovascular disease. Part I: Clinical features. Cephalalgia. 1992 12:269-274.
15. LP Savitz Levitan EB, Wears R, Edlow JA. Pooled analysis of patients with thunderclap headache evaluated by CT. Journal of Neurological Science 2009 15 276:123-125.
16. Perry JJ, Stiell IG, Sivilotti ML, Bullard MJ, Edmond M, Symington C, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid hemorrhage: prospective cohort study. BMJ. 2011;343:d4277.
17. Beek van de D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M: Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004 351:1849-1859

18. Raddant AC, Russo AF. Reactive oxygen species induce procalcitonin expression in trigeminal ganglia glia. Headache. 2014 54:472-84.

19. Gameiro J, Ferro JM, Canhão P, Stam J, Barinagarrementeria F, Lindgren A. Prognosis of cerebral vein thrombosis presenting as isolated headache: early vs. late diagnosis.; International Study on Cerebral Vein and Dural Sinus Thrombosis investigators. Cephalalgia. 2012 32:407-12.

Chapter 2

THE VALUE OF CT ANGIOGRAPHY IN PATIENTS WITH ACUTE SEVERE HEADACHE

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ABSTRACT

Background

Patients with acute severe headache may have a secondary form of headache. Standard head computer tomography (CT) and cerebrospinal fluid (CSF) examination are often performed in absence of neurological deficits to exclude subarachnoid hemorrhage (SAH). Increasingly patients undergo subsequent CT angiography (CTA) to exclude cerebral venous thrombosis (CVT), dissection or reversible cerebral vasoconstriction syndrome (RCVS). It is unknown whether this additional imaging increases diagnostic yield. We aimed to evaluate the yield of CTA in patients with acute severe headache with normal neurological examination and no abnormalities at standard CT and CSF analysis.

Methods

We included consecutive patients presenting to the emergency room between January 2008 and May 2011 with acute severe headache and without abnormalities at neurological examination, CT and CSF research, who received a CTA in the diagnostic process in our teaching hospital. All scans were re-reviewed by an experienced neuroradiologist.

Results

We included 70 patients, 71% were women and average age was 45 years. We found a vascular abnormality in 13 (19%) of our patients. Four had either a prior aneurysm or CVT. Eight patients had an unruptured intracranial aneurysm (UIA) on CTA (11%), 2 had CVT (3%), 2 had RCVS (3%) and 1 had cerebral ischemia (1%).

Conclusions

We found a high percentage of vascular abnormalities. A third of these patients had a prior episode of either an aneurysm or CVT. In patients with a history of UIA or CVT performing CTA despite normal CT and LP therefore seems warranted. A prospective study to delineate indications for CTA is needed.

BACKGROUND

Acute severe headache is defined as a headache of extreme severity that reaches its maximum within minutes and lasts for >1 hour. Acute severe headache may be a presenting symptom of, among others, a subarachnoid hemorrhage (SAH), cerebral venous thrombosis (CVT), arterial dissection, cerebral ischemia or reversible cerebral vasoconstriction syndrome (RCVS). Many studies have been published with regard to the correct sequence and content of diagnostic procedures. When standard CT is performed within six hours of the start of the headache SAH can be excluded, if performed in a center specialized in SAH. If CT is performed later, or if headache is atypical a lumbar puncture (LP) is still indicated [1,2]. However, in following this approach several diagnoses with severe consequences, other than SAH, may be missed. For example CVT may present with acute severe headache, without neurological deficit in 3-13% of cases [3,4]. Cervical arterial dissection has been reported to present with acute headache as the only symptom in 20% of cases [5,6]. Also, unruptured aneurysms are being reported as a possible cause of acute headache in several case reports [7-9]. RCVS has been reported to present with isolated headache in 57% to 88% of the cases [10].

CTA is increasingly used in patients with acute severe headache to rule out vascular abnormalities and has been proven valuable in detecting aneurysms [11]. To our knowledge there are no prospective studies investigating the gain of CTA in patients with acute severe headache, normal neurological exam and normal standard CT. One retrospective study that reviewed CTA in this group, found a higher percentage of vascular abnormalities (6.6%) than expected in the general population. However, lumbar punctures were not performed in that cohort. Also their study population was entirely Asian making extrapolation to our population difficult [12].

The risks of performing standard CTA include nephrotoxicity, added radiation exposure and allergic reactions. Furthermore, diagnostic procedures such as CTA increase costs. It is unclear whether these negative effects outweigh possible prevention of morbidity with a more aggressive screening approach. A study focusing on the added yield of CTA in patients with acute headache showed that CTA may be used selectively based on standard CT findings, thus increasing specificity and reducing patient risk [13]. We investigated the yield of CTA in patients with acute severe headache, without neurological deficit and a normal CT head and CSF for detecting vascular abnormalities.

PATIENTS AND METHODS

We performed a retrospective analysis researching the imaging findings of patients who presented at the emergency room in our large regional teaching hospital. These patients were previously described in a study focusing on cerebrospinal fluid (CSF) diagnostics [14]. For that

study we included patients from January 2008 through May 2011 with acute, non-traumatic, most severe ever, headache who underwent a lumbar puncture. For the present study we excluded patients with neurological deficits on examination, pathological findings on standard head CT, such as SAH or subdural hematoma, and patients with an increased bilirubin concentration (>0.2 µmol/l) in CSF. All imaging modalities were evaluated by specialized neuroradiologists at the time of presentation. The conclusions of the scans that were made at that time were collected. For this study all scans of included patients were re-reviewed by an experienced neuroradiologist. In accordance to hospital protocol CSF research was performed at least 12 hours after the onset of symptoms in all patients with normal standard CT. Collected samples were transported to the in-house laboratory and protected continuously from light. We documented and evaluated the outcome of performed CTA's. The CTA depicts both the arterial and venous system of intra- and extracranial vessels, by scanning the early and late phase of contrast passage. All patients underwent scanning by GE Lightspeed 64 slice CT scanner. Where available we also evaluated MRI and MRA data. Patient data were processed and descriptive statistics were done using SPSS 20.

RESULTS

Between January 2008 and May 2011, 361 patients presenting with acute and worst ever headache were seen in the emergency department. We included 70 patients who received a CTA and had normal neurological exam, normal CSF bilirubin and normal non-contrast CT's (see figure 1 for patient flow). All but one scan were made within a week of the occurrence of the headache; one scan was made after three weeks. All patients received CTA imaging of the head and the intra- and extracranial vessels down to the level of the fourth cervical vertebra and 31 patients were additionally scanned down to the aortic arch. Of our patients 50% received sufficient imaging of the cervical arteries to exclude dissection, including subsequent MRA.

The average age in this group was 45 years, ranging from 17 to 80 years old and 50 were women (71%). Nine patients had a prior history of migraines, eight had a history of tension type headache and the other 53 patients had no history of prior headaches. Of our patients 61 presented with generalized headache, in 19 there was unilateral headache. Nausea and vomiting were present in respectively 30 and 16 patients. Thirteen (19%) had a vascular abnormality, which had clinical consequences for ten patients (table 1). Eight had an aneurysm (11%, 95% CI: 4% to 19%). In three patients the aneurysm was coiled, in another three clipped and two patients received follow up CTA's to monitor aneurysm size. Four patients had small aneurysms of 2 and 3 mm and four patients had larger aneurysms ranging from 7.5 to 12mm. Three patients had been treated on a previous occasion after an SAH, but now had a second episode of acute headache and a de novo aneurysm. These aneurysms had not been seen on previous imaging. During our current revision they were not visible on previous scans either and were truly deemed de novo aneurysms. Of these de novo aneurysms one was also clipped and two were coiled. All three

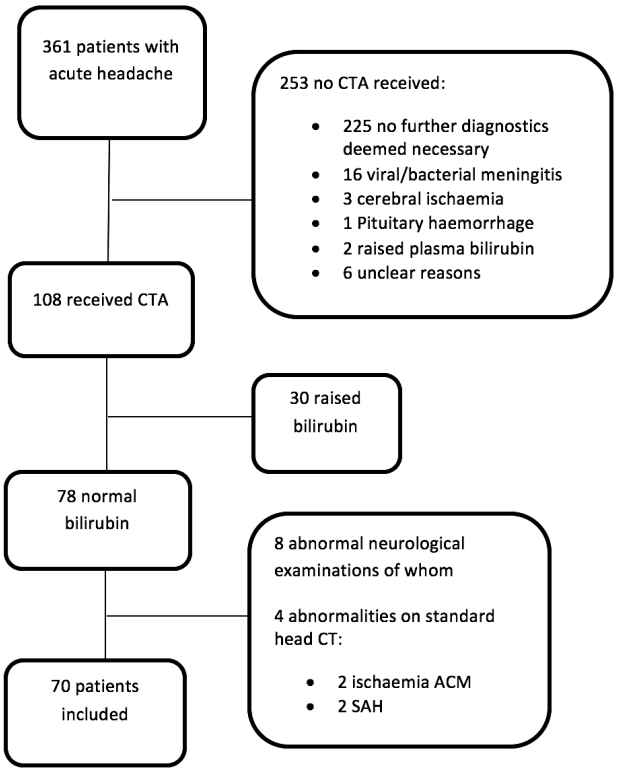

Figure 1. Patient inclusion flowchart

patients were included after the second headache episode. We found 2 patients with a CVT (3%) One patient with CVT had her diagnosis confirmed on MRA, as CTA findings were suspect. The other had a prior CVT and returned with a new episode of acute severe headache, nausea and vomiting. The CVT had progressed when compared to prior imaging. There were no other patients with a prior history of SAH or CVT, one patient had a prior, treated, AVM but now had normal CT, LP and CTA.

One patient had ischemia of the posterior circulation in the right occipital area. This patient presented with acute headache and non vertiginous dizziness. Ischemia was visible as this scan was performed two days later and had become demarcated.

Two patients had RCVS and were not diagnosed at initial presentation, but after reviewing the CTA's for this study. These were the only new abnormalities found by re-reviewing the scans. One patient presented with a single headache episode. The other visited again with another headache episode two days later, but remained undiagnosed at that time. Both did not revisit the emergency room or outpatient clinic after these episodes.

Table 1. Radiological findings and follow up in patients with pathology on CTA

Patient	Age	Sex	CT-A	Neurological history	Time to LP from headache onset	Follow up
	31	F	Right MCA aneurysm 2 mm	Right carotid top aneurysm	20 hours	Clipped
2	67	F	ACA aneurysm 3 mm		29 hours	CT follow up
3	62	M	MCA aneurysm 3 mm		Days, not specified	Clipped
4	54	F	Left MCA aneurysm 8 mm		Days, not specified	Coiled
5	61	F	A. com aneurysm 7.5 mm		One week	Coiled
6	58	F	P. com aneurysm 2 mm		36 hours	CT follow up
7	38	F	ICA aneurysm 7.5 mm	P. com aneurysm	1 day	Coiled
8	48	F	PCOM aneurysm 12 mm	A. opthalmica aneurysm	5 days	Coiled
9	37	M	CVT (2011)	CVT (2010)	Two weeks	Anticoagulant therapy
10	53	F	Cortical CVT	Ischemia left ACM territory	Three days	None
11	48	M	RCVS		Three weeks	None
12	30	F	RCVS		1 day	One episode of recurrent headache
13	73	M	Ischemia posterior circulation, right occipital area		1 day	Stroke follow up

Legend: ACA: anterior cerebral artery, MCA: middle cerebral artery, P. com Posterior communicating artery, A. com anterior communicating artery, ICA interior carotid artery, CVT cerebral venous thrombosis, RCVS reversible cerebral vasoconstriction syndrome

Of all 70 patients 15 patients underwent an additional MRI, four of whom had an aneurysm diagnosed with CTA and one of whom had CVT confirmed. In the remaining 10 patients who received MRI no pathology was found.

DISCUSSION

In this study we set out to evaluate the diagnostic yield of CTA in headache patients with a normal neurological examination, normal standard CT and normal lumbar puncture. With CTA we found a surprisingly high percentage of underlying vascular abnormalities (19%). Three patients had a prior SAH and one prior CVT. These findings had clinical consequences for ten patients.

In the general population the prevalence of aneurysms is estimated to be around 3.2% [15,16]. However, after correction for age and the percentage of women, the prevalence in our group should is calculated to be 3.6% [16]. Possibly this percentage is an underestimation as we have no data on family prevalence in our group and some patients had prior aneurysms. According to this prevalence we would have expected to find at least 3 aneurysms in our group of 70 patients. We found eight aneurysms (11%), with a 95% confidence interval from 4% to 19%. Half of the found aneurysms were small, but the other half were larger: up to 12mm. Whether the finding of an aneurysm caused the acute headache in our patients is debatable as lumbar punctures were normal. Nevertheless it has been suggested that unruptured aneurysms may cause headache due to inflammation or sudden distension. Three patients had a de novo aneurysm after treatment for prior aneurysmatic SAH. Two patients had CVT, one of whom had a prior CVT which had now progressed. Our study suggests that patients with prior SAH, and possibly CVT, should receive CTA despite normal CSF after a second episode of acute headache. In our group 5 patients had a prior history of cerebral vascular abnormalities. The four patients mentioned above and a patient with a history of a treated AVM who now had a normal CTA. This would mean 80% of the patients in our group of 70 with a history of cerebral vascular disease and a recurrent thunderclap headache had a de novo cerebral abnormality.

We found two patients with RCVS. This may be explained as cortical subarachnoid hemorrhage can be found in these patients, and the presence of abnormalities on standard head CT was an exclusion criterion in our study. Also RCVS may be more accurately diagnosed by repeated neuro-imaging and possibly MRA [17]. We found no dissections, which may be due to the fact that only 50% of patients received sufficient imaging of the carotid and vertebral arteries to exclude this diagnosis.

Our study has several limitations. First due to the retrospective design of our study there may be an indication bias. The patients with prior aneurysms and CVT are logical candidates for follow up by CTA, possibly increasing the chance of finding vascular abnormalities. Second this study is single center so our findings may not be generalizable. Tertiary headache centers may

find higher yield by referral bias, whereas primary centers may find lower percentages. The assessment of all clinical symptoms, such as detailed headache characteristics, was beyond the scope of this study.

One study with a similar design found 6.6% vascular lesions in 512 patients (33 aneurysms, 2 Moya Moya syndromes and 1 dissection), also suggesting value in performing CTA in this patient group [12]. The lower percentage of vascular abnormalities in that group compared to our findings may be partially explained by their exclusion of patients with prior intracranial vascular pathology. If these patients are excluded from our data, we still find 9 (14%) patients with vascular abnormalities. An important discrepancy with our methods is that lumbar punctures were not performed in this group to exclude hemorrhage, moreover, all their patients were Asian limiting the extrapolation of that study to our population.

Evidence from earlier studies suggests that patients with acute severe headache, without pathological findings on non-contrast CT and lumbar puncture do not require follow up, however, some if these studies did not perform CTA and focused mainly on SAH [18-22].

A prospective study performing CTA in patients with acute headache, normal neurological examination, normal head CT and normal lumbar puncture is needed, to investigate the yield of CTA and assess whether it is possible to make a selection for CTA for specific subgroups of patients based on clinical characteristics, thus reducing unnecessary exposure to radiation and intravenous contrast.

ETHICAL STANDARDS

As this was a retrospective study, without medical interventions, patient consent was not required according to hospital protocol and national guidelines.

REFERENCES

1. Perry JJ, Stiell IG, Sivilotti ML, Bullard MJ, Edmond M, Symington C, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid hemorrhage: prospective cohort study. BMJ. 2011;343:d4277.
2. Backes D, Rinkel GJ, Kemperman H, Linn FH, Vergouwen MD. Time-dependent test characteristics of head computed tomography in patients suspected of nontraumatic subarachnoid hemorrhage. Stroke. 2012; 43:2115-2119.
3. de Bruijn SF, Stam J, Kappelle. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet. 1996;348(9042):1623-1625.
4. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal Neurology Neurosurgery Psychiatry 2005;76(8):1084-1087.
5. Maruyama H, Nagoya H, Kato Y, et al. Spontaneous cervicocephalic arterial dissection with headache and neck pain as the only symptom. Journal Headache Pain. 2012 13(3):247-253.
6. Mitsias P, Ramadan NM Headache in ischemic cerebrovascular disease. Part I: Clinical features. Cephalalgia. 1992; 12(5):269-274.
7. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm Lancet. 1986 29;2(8518):1247-1248
8. Raps EC, Rogers JD, Galetta SL et al. The clinical spectrum of unruptured intracranial aneurysms. 1993; Arch neurology;50(3):265-268 .
9. Witham TF, Kaufmann AM. Unruptured cerebral aneurysm proceeding a thunderclap headache. Emergency Medicine. 2000 18(1):88-90
10. McCarron MO, Choudhari KA. Aneurysmal subarachnoid leak with normal CT and CSF spectrophotometry Neurology 2005 8;64(5):923.
11. Ducros A, Reversible vasoconstriction syndrome. Lancet Neurol 2012; 11: 906–17
12. Carstairs SD, Tanen DA, Duncan TD, et al. Computer tomographic angiography for the evaluation of subarachnoid hemorrhage. Academical Emergency Medicine 2006 13(5):486-492.
13. Han A, Yoon DY, Kim ES, Kim HC, Cho BM, Lee JY. Value of CT angiography for the detection of intracranial vascular lesions in patients with acute severe headache. Eur Radiol. 2013 Jun;23(6):1443-9.
14. Rizk B1, Platon A, Tasu JP, Becker CD, Mendes Pereira V, Perneger T, Shanmuganathan K, Lövblad KO, Poletti PA. The role of unenhanced CT alone for the management of headache in an emergency department. A feasibility study. J Neuroradiol. 2013 Dec;40(5):335-41.
15. Alons IME, Verheul RJ, Ponjee GA, Jellema K. Optimizing blood pigment analysis in cerebrospinal fluid for the diagnosis of subarachnoid hemorrhage - a practical approach. Eur J Neurol. 2013 Jan;20(1):193-7
16. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. New England Journal of Medicine. 2007;357(18):1821-8.
17. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurology. 2011;10(7):626-36

18. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome: a prospective series of 67 patients. Brain 2007; 130: 3091–101.
19. Wijdicks EF, Kerkhoff H, van Gijn J. Long-term follow-up of 71 patients with thunderclap headache mimicking subarachnoid haemorrhage. Lancet. 1988 9;2(8602):68-70.
20. Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. Brain. 2000 123 (Pt 2):205-221.
21. Söderström CE Diagnostic significance of CSF spectrophotometry and computer tomography in cerebrovascular disease. A comparative study in 231 cases. Stroke. 1977 8(5):606-12.
22. Vermeulen M, Hasan D, Blijenberg BG, Hijdra A, van Gijn. Xanthochromia after subarachnoid haemorrhage needs no revisitation. Journal of Neurology Neurosurgery Psychiatry. 1989 52(7):826-8.
23. LP Savitz Levitan EB, Wears R, Edlow JA. Pooled analysis of patients with thunderclap headache evaluated by CT Journal of Neurological Science 2009 15;276(1-2):123-125.

Chapter 3

YIELD OF CT ANGIOGRAPHY IN PATIENTS WITH ACUTE HEADACHE, NORMAL NEUROLOGICAL EXAMINATION AND NORMAL NON-CONTRAST CT: A META-ANALYSIS.

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ABSTRACT

Background

Patients with acute severe headache, normal neurological examination and a normal non-contrast head CT (NCCT) may still have subarachnoid hemorrhage (SAH), cerebral venous thrombosis (CVT), cervical arterial dissection or reversible cerebral vasoconstriction syndrome (RCVS). CT-angiography (CTA) is used increasingly in the emergency department (ED) for evaluating this, but its added value remains controversial.

Methods

We retrospectively collected data on the diagnostic yield of CTA in patients with acute severe headache, normal neurological examination and normal NCCT who received additional CTA in the acute phase in two secondary referral centers for vascular neurology. We combined data of our patients with those from the literature and performed a meta-analysis.

Results

We included 88 patients from our hospital files and 641 patients after literature search. Of 729 patients 54 had a vascular abnormality on CTA (7.4%; 95%CI 5.5-9.3%). Abnormalities consisted of aneurysms (n=42; 5.4%; 95%CI 3.8-7.0%), CVT (n=3, 0.5%), RCVS (n=4, 0.5%), Moya-Moya syndrome (n=2, 0.3%), arterial dissection (n=2, 0.3%) and ischemia (n=1, 0.1%). Because most of the aneurysms were probably incidental findings, only 12 (1.6%) patients had a clear relation between the headache and CTA findings. The number needed to scan to find an abnormality was 14 overall, and 61 for an abnormality other than an aneurysm.

Conclusion

Diagnostic yield of CTA in patients with acute headache, normal neurological examination and normal NCCT is low, but because of the possible therapeutic consequences its use might be justified in the emergency setting. Prospective studies confirming these results including cost-effectiveness analyses are needed.

INTRODUCTION

Acute headache may be the only presenting symptom of life threatening secondary headache syndromes. Patients with acute severe headache and a normal neurological examination may have subarachnoid hemorrhage (SAH), but also cerebral venous thrombosis (CVT), cervical arterial dissection (CAD) or reversible cerebral vasoconstriction syndrome (RCVS).[1-8]

Computer Tomographic Angiography (CTA) is increasingly used in the emergency setting for evaluating these important causes of secondary headache. CTA has been proven sensitive in determining the presence of aneurysms and CVT and to a lesser extent RCVS and dissections. [9,10] CTA has higher accessibility than MRI in most hospitals. Also cost and time reductions compared with MRI make it a possible valuable modality in evaluating ED patients, although CTA is more expensive than non-contrast head CT (NCCT) alone. There are other drawbacks of CTA. First, there is an added radiation exposure of approximately 2.5mSV after the NCCT which is also 2.5 mSV, with a total of 5 mSV.[11] Second, intra-venous (IV) iodinated contrast media may, rarely, cause allergic reactions and contrast nephropathy, particularly in patients with known nephropathy.[11,12]

The diagnostic yield of CTA in patients with acute headache and normal neurological examination and non-contrast head CT is unclear. A pooled analysis of follow up studies in patients with acute severe headache reported that in the group with normal non-contrast CT and normal lumbar puncture none had subsequent SAH. Based on these findings the authors advocated that CTA should not be used on a standard basis in these patients.[13] However, the included studies had a limited follow up period and in most patients CTA was not performed. Two large series of patients with acute headache concluded that if a NCCT is normal when performed within 6 hours of the start of the headache, a lumbar puncture is no longer needed due to the highly sensitive nature of third generation CT scanners.[15,16] This strategy is applicable to the exclusion of SAH, but because CTA was not performed in most patients, other diagnoses such as CVT, RCVS or CAD might have been missed. Two studies report percentages of vascular abnormalities ranging from 6.6 to 19%, in patients with acute severe headache, normal neurological examination and normal NCCT.[17,18] This is higher than may be expected in the general population. The first study was a large prospective study of 512 patients, but it was unknown whether lumbar punctures had been performed in these patients. In this study a large number of aneurysms was found, but it was not clear whether these were ruptured or unruptured intracranial aneurysms (UIA).[17] The second study from our own group had a limited size and patients were selected based on a normal lumbar puncture. This may have caused selection bias.[18]

The aim of our study was to evaluate the yield of CTA in patients presenting with acute severe headache to the (ED) in whom neurological examination and head NCCT was normal using both our own patient population and a meta-analysis of the literature.

METHODS

Own hospital data

We retrospectively evaluated data on all patients who underwent a cerebral CTA between 2011 and 2014 in the ED of the Leiden University Medical Center (LUMC), a tertiary vascular neurology referral center and university teaching hospital, and the MC Haaglanden, a secondary vascular referral center and primary teaching hospital. We included all patients who presented with acute headache, defined as headache that developed within 5 minutes and lasted for at least 1 hour.

In the Leiden University Hospital patients were scanned from the aortic arch up using the Aquilion One (Aquilion-ONE, Toshiba Medical Systems, Tokyo, Japan) and Aquilion 64 CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). In the MC Haaglanden patients were scanned from the aortic arch to the vertex with a GE Lightspeed 64-slice scanner.

We charted patient characteristics (age, sex, patient history and medication, seizures, loss of consciousness before admission, nausea, vomiting) and headache characteristics (location, duration, mode of onset, presence of aura, autonomous symptoms). We recorded results of CTA and other diagnostic procedures including lumbar punctures, digital subtraction angiography (DSA) and MRI when performed. Patients with focal neurological deficits, abnormalities on standard NCCT and, if performed, abnormal CSF findings (raised pressure and CSF chemistry showing hemorrhage or infection) were excluded. We recorded all adverse events that were possibly related to the CTA such as allergic reactions, kidney failure or infections after IV catheter use.

The study was approved by the local ethics committee and hospital board of both the LUMC and MC Haaglanden.

Literature search

The literature search was performed with Pubmed. Reference lists of relevant articles were scanned for further usable articles. Search terms were “acute headache”, “thunderclap headache”, “CT angiography”, “neuro-imaging”, “subarachnoid hemorrhage” and combinations thereof. We evaluated all articles published up to and including 2015.

Articles were included in the meta-analysis if they consisted of original articles including consecutive patients with acute, severe or worst ever headache who were evaluated by CTA. Case reports and case series were excluded to eliminate publication bias. Reviews and non-English articles were also excluded.

We charted CTA results and, when performed, results of MRI, LP and DSA. We also recorded adverse events possibly related to CTA.

All articles were read extensively and data were extracted with a data extraction form. If data were missing authors were contacted with the request for additional information.

RESULTS

Own Data

In the LUMC and MC Haaglanden 391 patients with acute headache who received a CTA were identified. Of the 391 patients 88 had a normal neurological examination and a normal NCCT. In 31 of the 88 patients a lumbar puncture was performed with normal results and 57 patients did not receive a lumbar puncture. A large number of patients had a history of migraine; 64 (73%). Eight patients had a history of SAH (9.5%). Four patients presented twice with acute headache. One presented twice within three months and was diagnosed with RCVS. The other three patients presented over a period of one year and were diagnosed with primary thunderclap headache. All other patients presented with first ever headache. Overall 5 patients (5.7%) had a vascular abnormality on CTA (Table 1, Patient characteristics). In 4 (4.5%) of these patients the abnormality was considered to be the cause of the headache, the other patient had a small unruptured aneurysm with a normal LP.

Literature

Through the Pubmed search a potential 1533 articles were identified . After elimination of duplicates, non-English articles, case reports, case series and reviews 482 articles remained. After scanning of titles and abstracts 12 potential articles were selected for further reading.[9, 17-26] Six articles met the inclusion criteria,[17-22] but only 3 articles gave sufficient information in order to ascertain the presence of a combination of a normal neurological examination, normal standard head CT and, if performed, a lumbar puncture without signs of hemorrhage. [17,18,20] Authors of the remaining three articles were contacted for additional information, however none of them responded.

A total of 641 patients were identified through literature search. Of these patients 49 had an abnormality on CTA (7.3%). (Table 2)

Combined data

We identified 729 patients with acute severe headache who met inclusion criteria. Average age was 46 years and there were 54.8% women. A CTA including the cervical arteries was performed in 182 patients. Fifty-four had an abnormality on CTA (7.4%; 95% CI 5.5-9.3%); table 3 provides an overview of abnormalities found. The patients with an abnormality on CTA had an average age of 50 years and 31 were women (57%). The abnormalities consisted of one patient with right occipital ischemia (0.1%), 2 cervical dissection (0.2%), two patients with abnormalities suspect for Moya-Moya syndrome (0.3%), three CVT (0.4%), four patients with RCVS (0.5%) and 42 cases with aneurysms (5.8%; 95% CI 4.1-7.5%). In nine out of 42 patients with an aneurysm a lumbar

Table 1. Patient characteristics own series

Characteristics	Patients (n=88)
Age (mean ± SD)	45.9±14.9
Women	63 (72%)
Neurological history	
Migraine	64 (73%)
Tension Type headache	14 (15.6%)
SAH	8 (9.5%)
Nausea	63 (72%)
Vomiting	33 (37.5%)
Aura	8 (9%)
<6h presentation at ER	23 (26%)
6-24h	30 (34%)
>24h	35 (40%)
CTA including cervical arteries	88 (100%)
Location headache	
Whole head	32 (36%)
Half-sided	5 (6%)
Localized	57 (65%)
Missing	3 (3%)
Type of headache	
Throbbing	15 (17%)
Stabbing	25 (28%)
Pressing	27 (31%)
Nagging	4 (4.5%)
Other	11 (12.5%)
Missing	15 (17%)
Adverse events CTA	1 (1%)
Abnormal CTA	5 (6%)
Aneurysm	1 (1%)
CVT	1 (1%)
RCVS	2 (2%)
Cervical Dissection	1 (1%)
MRI/MRA	
normal dissection	6 (7%)
Ischemia	1 (1%)
not performed	1 (1%)
Lumbar puncture	80 (91%)
normal	31 (35%)
not performed	57 (65%)

Legend: ER emergency room, CTA CT angiography, CVT cerebral venous thrombosis, RCVS reversible cerebral vasoconstriction syndrome

Table 2. Results meta-analysis, sex and age of patients

Study	Study type	No.	LP normal	CTA including cervical arteries	CTA abnormal	CT <6h after peak headache†	Sex (male)	Age yrs (mean)	MRI	DSA	Adverse Events	Diagnoses
Han et al [15]	Prospective	512	Not performed	0	34	Unknown	251 (49%)	46.2	-	15	0	31 aneurysms 1 dissection 2 Moya Moya
Rizk et al [18]	Prospective	59	Unknown	59	2	Unknown	-	-	-	-	-	2 UIA's
Alons et al. [16]	Retrospective	70	70	35	13	0	20 (29%)	45	15	4	0	8 aneurysms 2 CVT 2 RCVS 1 ischemia
Current study	Retrospective	88	31	88	5	2	32 (36%)	46	8	0	1	1 Aneurysm 1 CVT 2 RCVS 1 Dissection
Total		729	101	182	54	2	303 (45.2%)	46	23	19	1	42 aneurysms 2 dissections 2 Moya Moya 4 RCVS 3 CVT 1 Ischemia

Legend: LP lumbar puncture, MRI magnetic resonance imaging, CTA CT angiography, CVT cerebral venous thrombosis, RCVS reversible cerebral vasoconstriction syndrome, DSA digital substraction angiography, † Of patients with abnormal CTA

Table 3. Characteristics of patients with an abnormality on CTA

Number	Sex	Age	Study	Abnormality	Follow up
1	F	30	Han et al.	Aneurysm, ICA 3.4mm	Clinical FU
2	M	56	Han et al.	Aneurysm, ICA 2.7mm	Clinical FU
3	F	35	Han et al.	Aneurysm, ICA, 4.2 mm	Clinical FU
4	M	52	Han et al.	Aneurysm, ICA, 3.5 mm	Clinical FU
5	F	71	Han et al.	Aneurysm, ICA, 9.4 mm	Refused treatment
6	F	70	Han et al.	Aneurysm, ICA, 3.3 mm	Clip ligation
7	F	27	Han et al.	Aneurysm, ICA, 3.8 mm	Follow-up with CTA
8	F	50	Han et al.	Aneurysm, ICA, 2.0 mm	Clinical FU
9	M	56	Han et al.	Aneurysm, ICA, 2.6 mm	Follow-up with CTA
10	F	67	Han et. al.	Aneurysm, ICA, 2.0 mm	Clinical FU
11	F	40	Han et al.	Aneurysm, ICA, 2.9 mm	Clinical FU
12	F	42	Han et al.	Aneurysm, ICA, 2.8 mm	Clinical FU
13	M	47	Han et al.	Aneurysm, AcomA, 3.0 mm	Clip ligation
14	F	41	Han et al.	Aneurysm, AcomA, 13.1 mm	Coil insertion
15	M	37	Han et al.	Aneurysm, AcomA, 3.5 mm	Refused treatment
16	F	57	Han et al.	Aneurysm, AcomA, 5.6 mm	Clip ligation
17	F	68	Han et al.	Aneurysm, AcomA, 2.5 mm	Clinical FU
18	M	61	Han et al.	Aneurysm, AcomA, 2.7 mm	Clinical FU
19	M	48	Han et al.	Aneurysm, AcomA, 4.6 mm	Coil insertion
20	M	80	Han et al.	Aneurysm, MCA, 6.9 mm	Clip ligation
21	M	64	Han et al.	Aneurysm, MCA, 2.5 mm	Clinical FU
22	F	55	Han et al.	Aneurysm, MCA, 2.1 mm	Follow up with CTA
23	M	46	Han et al.	Aneurysm, MCA, 2.0 mm	Clinical FU
24	F	55	Han et al.	Aneurysm, MCA, 2.1 mm	Clinical FU
25	F	65	Han et al.	Aneurysm, MCA, 3.0 mm/ACA, 2.5 mm	Clinical FU
26	M	33	Han et al.	Aneurysm, PcomA, 3.5 mm	Coil insertion
27	F	23	Han et al.	Aneurysm, PcomA, 4.0 mm	Coil insertion
28	M	49	Han et al.	Aneurysm, PcomA, 2.7 mm	Follow up with CTA
29	F	51	Han et al.	Aneurysm, PcomA, 3.0 mm	Clinical FU
30	M	54	Han et al.	Aneurysm, PcomA, 11.0 mm/MCA, 3.0 mm	Coil insertion
31	F	53	Han et al.	Aneurysm, BA, 3.3 mm	Refused treatment

Table 3. Continued

Number	Sex	Age	Study	Abnormality	Follow up
32	M	37	Han et al.	Dissection, VA	Medication change
33	F	50	Han et al.	Moya Moya disease	Follow up with MRA
34	M	32	Han et al.	Moya Moya disease	Follow up with MRA
35	F	31	Alons et al.	Aneurysm, MCA, 2 mm	Clip ligation*
36	F	67	Alons et al.	Aneurysm, AcomA, 3 mm	Follow up with CTA*
37	M	62	Alons et al.	Aneurysm, MCA, 3 mm	Clip ligation*
38	F	54	Alons et al.	Aneurysm, MCA, 8 mm	Coil insertion*
39	F	61	Alons et al.	Aneurysm, AcomA, 7.5 mm	Coil insertion*
40	F	58	Alons et al.	Aneurysm, PcomA, 2 mm	Follow up with CTA*
41	F	38	Alons et al.	Aneurysm, ICA, 7.5 mm	Coil insertion*
42	F	48	Alons et al.	Aneurysm, Pcom, 12 mm	Coil insertion*
43	M	37	Alons et al.	CVT transverse and sagittal sinus	Anti-coagulant therapy
44	F	53	Alons et al.	Cortical vein thrombosis	None
45	M	48	Alons et al.	RCVS	None
46	F	30	Alons et al.	RCVS	One recurrent episode
47	M	73	Alons et al.	Ischaemia right occipital lobe	Medication change
48	-	-	Rizk et al.	UIA	Follow up with imaging
49	-	-	Rizk et al.	UIA	Follow up with imaging
50	F	51	Current study	Aneurysm, MCA,10 mm	Clip ligation*
51	M	42	Current study	RCVS	Clinical follow up†
52	M	42	Current study	RCVS	Clinical follow up†
53	F	36	Current study	CVT	Medication Change
54	M	46	Current study	Dissection left ICA	Medication change

Legend: ICA internal carotid artery, Acom Anterior communal artery, MCA medial carotid artery, PcomA posterior communal artery, BA basilar artery, VA vertebral artery, CVT cerebral venous thrombosis, RCVS reversible cerebral vasoconstriction syndrome, UIA unruptured intracranial aneurysm. * lumbar puncture normal, † CT<6 hours after peak headache

puncture was performed, which showed no signs of hemorrhage in none of these patients. Of the remaining 33 patients no data on whether an LP was performed or outcome of LP were found. Of the 42 patients with an aneurysm, 25 patients received either coiling or clipping of an aneurysm.

Four patients received altered medical treatment concerning CVT or stroke. Of the remaining patients, 23 received either clinical or imaging follow up. The number needed to scan for finding an abnormality likely causative of the acute headache was 61. In 12 patients (1.6%) there was a clear relation with the acute headache. When one considers unruptured aneurysms to be clinically relevant, the number needed to scan is 14 (n=54).

One patient in this series had an adverse event, an allergic reaction to contrast iodinated contrast media, with reversible effect and short term harmful effects for the patient.

DISCUSSION

In our meta-analysis an vascular abnormality was identified with CTA in 7.4% of patients with acute severe headache and a normal neurological examination and NCCT of the head. In 12 (1.6%) patients this abnormality was presumably the cause of the headache.

The number of aneurysms found is slightly higher than might be expected in the general population. This number is dependent on the percentage of women and the average age. For all patients described here the expected percentage would be 3.2%.[27]

The question remains whether these aneurysms are of clinical significance. If an aneurysm has not actively bled it is probably not the cause of the acute headache, but an incidental finding. An LP is necessary to rule out hemorrhage. However, in a large proportion of patients with an aneurysm in this series the outcome of the LP was unknown and therefore we cannot determine if the aneurysm had ruptured or not. Radiological follow-up may be offered to patients with an unruptured intracranial aneurysm, however, it is unknown if such a follow-up strategy is cost-effective. The necessity to treat an aneurysm depends on the estimated risk of rupture, which in turn depends on patient factors such as age, hypertension, location of the aneurysm, previous SAH and ethnicity of the patient. [28] As not all factors were known to us in this patient group, the necessity of treatment of the detected aneurysms could not be determined. A considerable number of patients with aneurysms in this series has been treated but because we were unaware of the indication of treatment we cannot confirm that they are clinically relevant.

We found a surprisingly low number of patients with RCVS. In a recent paper RCVS was found in 8.8% of the patients using MRI/MR angiography. It is likely that CTA is not the ideal modality for diagnosing this condition. Also it is postulated that RCVS may only be seen on imaging in

a later stage and repeated imaging improves sensitivity. [9] Cervical artery dissection is often suspected in patients with acute headache. In this series only 2 of the 182 patients who received CTA including the carotid and vertebral arteries had a cervical artery dissection (1.1%; 95% CI -0.4-2.6%). Our data suggest that it is a relatively rare cause of secondary headache, but since not all patients had a CTA from the aortic arch, this may be an underestimate.

In this patient group there was only one recorded adverse event; an allergic reaction to iodinated contrast media, with reversible effect and short term harmful effects for the patient. Possible adverse events after CTA are nephrotoxicity and allergic reactions to iodinated contrast media. [12,13] It is likely that in this group of relatively young patients, with little comorbidity, renal function is good thus reducing the risk of nephrotoxicity. The chance of contrast nephropathy in patients receiving CTA after acute stroke is low and reported to be 2-3.2% including only mild, reversible nephropathy.[12,13] Underreporting may have also affected these numbers, as nefrotoxicity was not systematically checked in this retrospective series. The added radiation exposure after CTA is on average 2.5mSv per patient. This is equal to 20 months of background radiation. There is a debate how radiation exposure due to head CT alters the risk of cancer. One study evaluating pediatric patients after 10 years of follow up after head CT, concluded that the risk of development of a malignant brain tumor was not raised. However, there was an increased risk of development of benign brain tumors.[29] In this study the reason for the CT study was unknown. Therefore, 'reverse causation' may blur results and give cause to a higher reporting of cancer rates than caused by added radiation exposure alone. Another large, recent study concluded that the risk of leukemia was tripled when doses exceeding 50mSv were given. [30] Moreover, the risk of brain tumor was tripled when doses of more than 60mSv were given. These doses are nowhere near the dose given for a single CTA. The risk of cancer induction from a single combined brain/cervical CTA seems therefore negligible and to outweigh the risk of a missed vascular cause of acute headache.

This is the largest study on the yield of CTA in the group of patients with acute headache, normal neurological examination and normal NCCT. By performing a meta-analysis we improved the generalizability and precision of our results.

Our study has limitations. First, we were dependent on studies of varying methodology and with varying diagnostic goals and thus the indication for performed CTA may not be completely clear and patient series may not have been consecutive. Secondly, not all patient data from studies eligible for inclusion could be retrieved, limiting the number of available patients. Unfortunately, despite repeated requests additional information was not obtained from three studies. Our added data were collected retrospectively and therefore an indication bias for performing CTA might have occurred. We cannot deduce how many patients with acute headache did not receive a CTA.

The chance of a finding with clinical implications in the group of patients with acute headache, normal examination and normal non-contrast CT is low. However, as any finding of CVT and dissection warrants medication change and follow up, the finding of these diagnoses has high clinical relevance. RCVS is deemed self-limiting, however consequences of this condition may be severe. The number needed to scan in our series to find a clinically relevant abnormality (e.g. the probable cause of headache) on CTA, was 61, the number needed to scan to find any abnormality was 14. There was only one recorded complication and radiation from CTA is relatively low. We therefore conclude that the diagnostic yield of CTA in patients with acute headache, normal neurological examination and normal non-contrast head CT is limited but because of the consequences for treatment high enough to justify the possible adverse events. However, prospective studies to confirm these findings are needed.

REFERENCES

1. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal Neurology Neurosurgery Psychiatry 2005;76:1084-1087.
2. Maruyama H, Nagoya H, Kato Y, et al. Spontaneous cervicocephalic arterial dissection with headache and neck pain as the only symptom. Journal Headache Pain. 2012 13(3):247-253.
3. Mitsias P, Ramadan NM Headache in ischemic cerebrovascular disease. Part I: Clinical features. Cephalalgia. 1992; 12:269-274.
4. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm Lancet. 1986 29;2:1247-1248
5. Raps EC, Rogers JD, Galetta SL et al. The clinical spectrum of unruptured intracranial aneurysms. Arch neurology; 1993:50:265-268 .
6. Witham TF, Kaufmann AM. Unruptured cerebral aneurysm proceeding a thunderclap headache. Emergency Medicine. 2000 18:88-90
7. McCarron MO, Choudhari KA. Aneurysmal subarachnoid leak with normal CT and CSF spectrophotometry Neurology 2005 8;64:923.
8. Ducros A. Reversible vasoconstriction syndrome. Lancet Neurol 2012; 11: 906–17
9. Grooters GS, Sluzewski M, Tijssen CC, How often is thunderclap headache caused by the reversible cerebral vasoconstriction syndrome? Headache. 2014;54:732-5.
10. Provenzale JM1, Sarikaya B. Comparison of test performance characteristics of MRI, MR angiography, and CT angiography in the diagnosis of carotid and vertebral artery dissection: a review of the medical literature. AJR Am J Roentgenol. 2009;193:1167-74.
11. Cohnen M, Wittsack HJ, Assadi S, Muskalla K, Ringelstein A, Poll LW, et al. Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. AJNR Am J Neuroradiol. 2006; 27:1741-5.
12. R. Dittrich, S. Akdeniz, , S. P. Kloska, et al. Low rate of contrast-induced Nephropathy after CT perfusion and CT angiography in acute stroke patients. Journal of Neurology 2007: 1491-1497
13. Luitse MJA, Dauwan M, van Seeters T et al. Acute Nephropathy after Contrast Agent Administration for Computed Tomography Perfusion and Computed Tomography Angiography in Patients with Acute Ischemic Stroke. Int J Stroke. 2015 10:E35-6
14. LP Savitz Levitan EB, Wears R, Edlow JA. Pooled analysis of patients with thunderclap headache evaluated by CT. Journal of Neurological Science 2009 15; 276:123-125
15. Perry JJ, Stiell IG, Sivilotti ML, Bullard MJ, Edmond M, Symington C, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid hemorrhage: prospective cohort study. BMJ. 2011; 343:d4277.
16. Backes D, Rinkel GJ, Kemperman H, Linn FH, Vergouwen MD. Time-dependent test characteristics of head computed tomography in patients suspected of nontraumatic subarachnoid hemorrhage. Stroke. 2012; 43:2115-2119.

17. Han A, Yoon DY, Kim ES, Kim HC, Cho BM, Lee JY. Value of CT angiography for the detection of intracranial vascular lesions in patients with acute severe headache. Eur Radiol. 2013; 23:1443-9.

18. Alons IM, van den Wijngaard IR, Verheul RJ, et al. The value of CT angiography in patients with acute severe headache. Acta Neurol Scand. 2015;131(3):164-8

19. Jamshidi S, Kandiah PA, Singhal AB, et al. Clinical predictors of significant findings on head computed tomographic angiography. J Emerg Med. 2011;40:469-75.

20. Rizk B, Platon A, Tasu JP, et al. The role of unenhanced CT alone for the management of headache in an emergency department. A feasibility study. J Neuroradiol. 2013;40:335-41.

21. Carstairs SD, Tanen DA, Duncan TD, et al. Computed tomographic angiography for the evaluation of aneurysmal subarachnoid hemorrhage. Acad Emerg Med. 2006;13:486-92.

22. Thomas LE, Czuczman AD, Boulanger AB, et al. Low risk for subsequent subarachnoid hemorrhage for emergency department patients with headache, bloody cerebrospinal fluid, and negative findings on cerebrovascular imaging. J Neurosurg. 2014;121:24-31.

23. Brunell A, Ridefelt P, Zelano J. Differential diagnostic yield of lumbar puncture in investigation of suspected subarachnoid haemorrhage: a retrospective study. J Neurol (2013) 260:1631–1636.

24. Landtblom AM, Fridriksson S, Boivie J , Hillman J, Johansson G, Johansson I. Sudden onset headache: a prospective study of features, incidence and causes. Cephalalgia 2002;22:354–360.

25. Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008;52:407-36

26. Renou P, Tourdias T, Fleury O, Debruxelles S, Rouanet F, Sibon I. Atraumatic nonaneurysmal sulcal subarachnoid hemorrhages: a diagnostic workup based on a case series. Cerebrovasc Dis. 2012;34:147-52.

27. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurology. 2011;10:626-36

28. Greving JP, Wermer MJ, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol.2014;(1):59-66.

29. WY Huang, CH Muo, CY Lin, YM Jen, MH Yang, JC Lin, FC Sung, CH Kao. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. British Journal of Cancer (2014) 110, 2354–2360

30. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 4;380:499-505

Chapter 4

PREDICTION OF VASCULAR ABNORMALITIES ON CT ANGIOGRAPHY IN PATIENTS WITH ACUTE HEADACHE

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ABSTRACT

Objectives

Patients with acute headache increasingly undergo CT-angiography (CTA) to evaluate underlying vascular causes. The aim of this study is to determine clinical and non-contrast CT (NCCT) criteria to select patients who might benefit from CTA.

Methods

We retrospectively included patients with acute headache who presented to the emergency department of an academic medical center and large regional teaching hospital and underwent NCCT and CTA. We identified factors that increased the probability of finding a vascular abnormality on CTA, performed multivariable regression analyses and determined discrimination with the C-statistic.

Results

A total of 384 patients underwent NCCT and CTA due to acute headache. NCCT was abnormal in 194 patients. Among these, we found abnormalities in 116 cases of which 99 aneurysms. In the remaining 190 with normal NCCT we found abnormalities in 12 cases; four unruptured aneurysms, three cerebral venous thrombosis', two reversible cerebral vasoconstriction syndromes, two cervical arterial dissections and one cerebellar infarction. In multivariable analysis abnormal NCCT, lowered consciousness and presentation within 6 hours of headache onset were independently associated with abnormal CTA. The c-statistic of abnormal NCCT alone was 0.80 (95%CI: 0.75-0.80), that also including the other two variables was 0.84 (95%CI: 0.80-0.88). If NCCT was normal no other factors could help identify patients at risk for abnormalities.

Conclusions

In patients with acute headache abnormal NCCT is the strongest predictor of a vascular abnormality on CTA. If NCCT is normal no other predictors increase the probability of finding an abnormality on CTA and diagnostic yield is low.

INTRODUCTION

Acute headache may have several vascular causes including subarachnoid hemorrhage (SAH) from a ruptured aneurysm, cerebral venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS) or arterial dissection[1-8]. These vascular abnormalities can be diagnosed in the emergency setting with CT angiography (CTA).

An additional CTA causes excess radiation exposure of 2.5 mSv after normal NCCT (which also causes 2.5mSv[9]). The iodine contrast which is given intravenously may cause allergic reactions and contrast nephropathy in a small number of cases[9-11]. Therefore, discriminating clinical characteristics such as abnormalities on neurological examination to more selectively apply CTA would be valuable for physicians in reducing unnecessary diagnostic tests.

Previous research focused on the value of CTA of the brain and cervical arteries in all emergency department patients[12] or on development of a clinical decision rule for diagnosing SAH, regardless of CTA results, in patients with acute headache[13]. These studies found that several characteristics such as signs of hemorrhage on non-contrast head CT (NCCT), deficit on neurological examination, acute onset of headache[12], age over 40 years, nuchal rigidity or onset during exertion[13] are associated with a higher risk of abnormalities on CTA or the chance of SAH. A clinical prediction rule for vascular abnormalities on CTA for patients in the emergency department with acute headache and a normal NCCT is currently not available.

In this study we evaluated patients presenting with acute headache in whom CTA was performed to exclude secondary forms of headache. We aimed to develop a diagnostic prediction model with headache, patient and NCCT characteristics to identify patients with the highest probability of an abnormality on CTA.

MATERIALS AND METHODS

We retrospectively evaluated all patients who underwent a cerebral and cervical CTA between January 2011 to December 2014 in the emergency department of the Leiden University Hospital (LUMC), a tertiary vascular neurology referral center and university teaching hospital, and the Haaglanden Medical Centre in The Hague, a tertiary vascular referral center and a secondary teaching hospital. We included all patients who presented with acute headache. We defined acute headache as headache peaking within 5 minutes and lasting more than 1 hour. We excluded patients who were comatose (EMV <9), who had an ongoing seizure or were otherwise unable to express whether they had headache. Patients were also excluded when their headache developed after a trauma or after start of focal neurological deficits.

The patients were identified in the hospital digital medical chart system by evaluating all patients who received a cerebral and cervical CTA and were admitted to the emergency department. All medical charts were reviewed for the in- and exclusion criteria. Chart review was done by IMA and BFJG with a standardized data abstraction form. We charted patient characteristics (age, sex, patient history and medication, focal neurological deficits, seizures, loss of consciousness ongoing or of short duration not deemed a seizure, nausea, vomiting, nuchal rigidity, papillary edema) and headache characteristics (location, duration, presence of aura, autonomous symptoms).

In the Leiden University Hospital patients were scanned from the aortic arch up to the vertex with an Aquilion One (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) or Aquilion 64 CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). In the MC Haaglanden patients were scanned from the aortic arch to the vertex with a General Electrics Lightspeed 64-slice scanner (General Electric, Chicago Il, USA).

We recorded adverse events of the CTA including allergic reactions, kidney failure or infections after IV catheter use. The adverse events were deducted from the authorized hospital form used to chart any clinical adverse events during admission.

The study was evaluated and approved by the local ethics committee, which waived the need for patient consent as all data were recorded anonymously.

Statistical analysis

We calculated prevalence ratios with corresponding 95% confidence intervals for patient characteristics in relation to presence of abnormalities at CTA. Multivariable logistic regression analysis was performed with a vascular abnormality at CTA as the outcome variable. Candidate predictors were considered for entrance into multivariable regression models irrespective of their univariable association with a vascular abnormality at CTA[14]. We included all candidate predictors in the multivariable logistic regression model and excluded them stepwise when the likelihood ratio test had $p>0.15$. The discriminative performance, to which the prognostic model enables discrimination between patients with and without vascular abnormalities at CTA, was described by the c-statistic. The c-statistic varies between 0.5 (a non-informative model) and 1.0 (a perfect model)[15]. Our report on prediction adheres to the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) guidelines[16]. This guideline consists of a 22 item checklist detailing the essential information that should be included in a report of a prediction modeling study.

Some variables, such as papillary edema or nuchal rigidity, were not recorded and thus missing in some cases. The absence of these the clinical signs in the examination was also evaluated to ascertain whether this was a predictive factor.

RESULTS

We included 384 patients (flowchart 1). The average age of the participants was 51 years and 150 (39.1%) were men. In the entire group of patients 129 presented with a normal neurological examination (33.6%), 190 had a normal NCCT (49.4%) and 128 had an abnormality on CTA (33.3%). Other characteristics can be found in table 1.

Patients with abnormal NCCT

Of the 194 patients with an abnormal NCCT there were 116 with an abnormality on CTA (59.8%) (figure 1). All these abnormalities were symptomatic and were treated accordingly. 128 (74.1%)

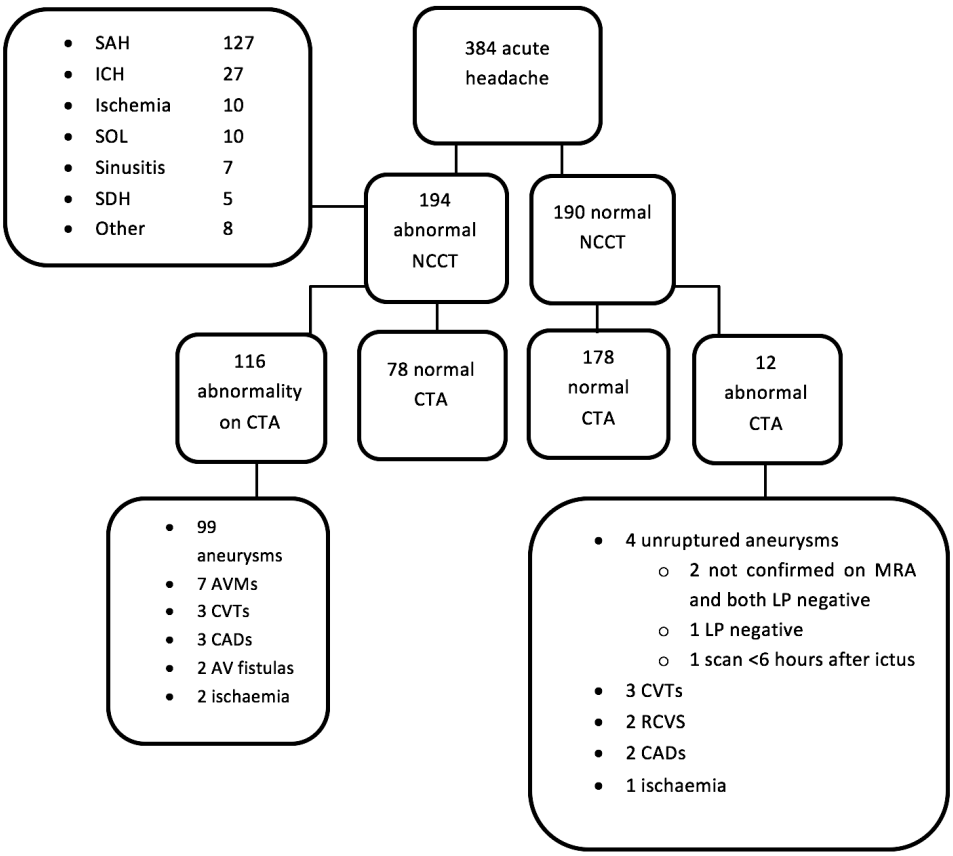

Figure 1. Patient inclusion flowchart.
Legend: ED emergency department, NCCT non-contrast CT, CTA CT angiography, CVT cerebral venous thrombosis, AVM arterio-venous malformation, LP Lumbar puncture, RCVS reversible cerebral vasoconstriction syndrome, CAD cervical arterial dissection, IH intraparenchymal hemorrhage, SOL space occupying lesion

Table 1. Characteristics of the 384 included patients

Characteristic	No. (%)
Age (years)	51; SD 15
Male sex	150 (39.1%)
Duration to presentation (days ave)	2.4; SD 4.9
Headache location	
Halfsided	30 (7.8%)
Whole head	161 (41.6%)
Localised	193 (50.3%)
Nausea	97 (25.1%)
Vomiting	186 (48.4%)
Neurological examination	
Normal	129 (33.6%)
Abnormal	255 (66.4%)
Subjective deficit	97 (25.3%)
Motor lateralisation	42 (10.9%)
Sensory lateralisation	29 (7.5%)
Papillary edema	6 (0.1%)
Abnormal pupils	23 (5.9%)
Nuchal rigidity	44 (11.5%)
NCCT	
Normal	190 (49.4%)
SAH	128 (33.1%)
Intraparenchymal hemorrhage	32 (8.3%)
Ischemia	11 (2.8%)
Space occupying lesion	10 (2.6%)
Sinusitis	7 (1.8%)
SDH	2 (0.5%)
Other	4 (1%)
CTA	
Normal	256 (66.7%)
Aneurysm	103 (26.8%)
CVT	6 (1.6%)
AVM	7 (1.8%)
Dissection	5 (1.3%)
Ischemia	3 (0.7%)
RCVS	2 (0.5%)
AV fistula	2 (0.5%)

Table 1. Continued

Characteristic	No. (%)
LP	
Not performed	287 (74.7%)
Normal	69 (18%)
Hemorrhage	14 (3.6%)
Meningitis	10 (2.6%)
Raised pressure	4 (1%)

Legend: NCCT non contrast CT, SAH subarachnoid hemorrhage, SDH subdural hematoma, CTA CT angiography, CVT cerebral venous thrombosis, AVM arterio-venous malformation, RCVS reversible cerebral vasoconstriction syndrome, LP lumbar puncture.

patients had SAH on NCCT and in 96 (95.1%) of these patients an aneurysm was found. In two patients the CTA showed no abnormalities but an aneurysm was detected after MRI and digital subtraction angiography. Three patients with an intraparenchymal hemorrhage also had a causative aneurysm on CTA. The number needed to scan to find a clinically relevant vascular abnormality on CTA in this group was less than 2 patients (1.7).

Patients with normal NCCT

In 190 patients (49.5%) the NCCT was normal. Twelve (6.3%) of these patients had a vascular abnormality on CTA and in seven (3.7%) of these patients the abnormality was thought to be the cause of the headache. These seven abnormalities were also of clinical significance because they warranted a change of medication or more intensified follow up. We could not define whether the found aneurysms were relevant because we did not have sufficient data to retrieve if they had ruptured or not. Unruptured aneurysms are not a likely cause of headache and may be an incidental finding. Also data on the necessity of treatment according to our guidelines were not completely available. Three patients had CVT, one of which had been diagnosed earlier and was unchanged; we did not count this as a relevant finding. Two patients were diagnosed with RCVS, two with a cervical arterial dissection and one with a cerebellar infarction. Thus the number needed to scan to find a clinically relevant abnormality was 27.

In addition to the clinically relevant findings, unruptured aneurysms were found in four patients; in two patients the aneurysms could not be confirmed on MRI, one patient with an MRI confirmed aneurysm had a normal LP and the fourth patient did not receive an LP but presented within 6 hours on the ED, with normal NCCT ruling out SAH.

Table 2. Abnormality at CTA in relation to patient characteristics in 384 included patients

	% abnormal CTA		
Patient characteristics	**Baseline characteristic present (n/N (%))**	**Baseline characteristic absent (n/N (%))**	**Prevalence ratio (95% CI)**
Age 45-65 years	71/183 (38.8%)	21/119 (17.6%)*	2.20 (1.43-3.38)
Age ≥65 years	36/82 (43.9%)	21/119 (17.6%)*	2.49 (1.57-3.94)
Female sex	79/234 (33.8%)	49/150 (32.7%)	1.03 (0.77-1.38)
Presentation <6h	83/179 (46.4%)	44/204 (21.6%)	2.15 (1.58-2.92)
Unilateral headache	3/30 (10.0%)	125/354 (35.3%)	0.28 (0.10-0.84)
Aura	3/21 (14.3%)	84/296 (28.4%)	0.50 (0.17-1.46)
No Aura recorded	41/67 (61.2%)	87/317 (27.4%)	2.23 (1.72-2.90)
Vomiting	38/186 (20.4%)	76/172 (44.2%)	0.46 (0.33-0.64)
Seizure	3/8 (37.5%)	125/376 (33.2%)	1.13 (0.46-2.79)
Collaps	12/23 (52.2%)	116/361 (32.1%)	1.62 (1.07-2.47)
Altered mental state	4/7 (57.1%)	124/377 (32.9%)	1.74 (0.90-3.35)
Impaired consciousness	24/33 (72.7%)	104/351 (29.6%)	2.45 (1.89-3.20)
Normal glascow coma scale	82/309 (26.5%)	46/75 (61.3%)	0.43 (0.33-0.56)
Nuchal rigidity	25/44 (56.8%)	73/291 (25.1%)	2.26 (1.64-3.14)
Subjective neurological deficit	39/97 (40.2%)	84/282 (29.8%)	1.35 (1.00-1.83)
Pupillary responses abnormal	14/24 (58.3%)	109/353 (30.9%)	1.89 (1.30-2.74)
Motor deficit	19/42 (45.2%)	105/338 (31.1%)	1.46 (1.01-2.11)
Sensory deficit	10/29 (34.5%)	113/350 (32.3%)	1.07 (0.63-1.80)
Neurological examination normal	22/129 (17.1%)	106/255 (41.6%)	0.41 (0.27-0.62)
Non Contrast CT normal	12/190 (6.3%)	116/194 (59.8%)	0.11 (0.06-0.18)
Lumbar puncture normal	6/69 (8.7%)	6/29 (20.7%)	0.42 (0.15-1.20)
Lumbar puncture hemorrhage	4/14 (28.6%)	8/84 (9.5%)	3.00 (1.04-8.65)
Lumbar puncture infectious	1/10 (10%)	11/88 (12.5%)	0.80 (0.12-5.67)
Lumbar puncture raised pressure	1/4 (25%)	11/94 (11.7%)	2.14 (0.36-12.74)
Neurological history	17/46 (37.0%)	106/333 (31.8%)	1.16 (0.77-1.75)
Headache history	19/82 (23.2%)	106/299 (35.5%)	0.65 (0.43-1.00)

*Age <45 years was taken as a reference

Multivariable analyses

In the univariable analyses of all 384 patients there were 14 variables associated with either CTA abnormalities or normal CTA. Age, presentation within 6 hours of headache, vomiting, collapse, impaired consciousness, nuchal rigidity, subjective neurological deficit, abnormal pupillary responses, motor deficit were associated with abnormal CTA. Normal NCCT, unilateral headache, normal neurological examination, normal Glasgow Coma Score and a history of previous headaches were associated with normal CTA (Table 2).

In the multivariate analyses three factors were significantly associated with an abnormal CTA: presentation within 6 hours of headache, abnormal NCCT and ongoing impaired consciousness at time of the NCCT (table 3). The c-statistic of this model was 0.84 (95%CI: 0.80-0.88). A model based on clinical characteristics only contained 7 variables (presentation <6h, half sided headache, aura, vomiting, nuchal rigidity, pupil abnormalities, and lumbar puncture performed) and had a c-statistic of 0.80 (95% CI 0.76-0.85). A model based on NCCT alone had a c statistic of 0.80 (0.75-0.85). The difference between the c-statistics was not statistically significant.

We attempted to assess which factors would be related to an abnormal CTA in the 190 patients with a normal NCCT. However, because there were only 12 patients with a CTA abnormality in this group we could not identify these factors as overall yield was low.

Table 3. Multivariable model on basis of clinical characteristics and NCCT

	Odds ratio	95% CI
Presentation < 6h	1.82	1.06-3.12
Normal consciousness	0.46	0.24-0.86
Normal NCCT	0.06	0.03-0.11
C statistic	0.84	0.80-0.88

DISCUSSION

We found that the yield of CTA in patients with acute headache presenting at the emergency department and an abnormal NCCT is high. An abnormal NCCT was the strongest predictor for finding an abnormality on CTA. When combined with the two other clinical factors that contributed independently to finding an abnormal CTA, an impaired lowered consciousness and presentation within 6 hours of headache, discrimination was not better than when NCCT alone was used. In patients with normal NCCT the diagnostic yield was low and in only seven out of 190 patients a clinical relevant abnormality was found.

As far as we are aware this is the first study focusing on a prediction model for finding an abnormality on CTA in acute headache focusing on a broader diagnostic range than just SAH. We included patients from an academic medical center and a large teaching hospital to improve the generalizability of our results.

Our study has several limitations. First, there is a likely selection bias in the performed CTAs limiting the number of CTAs in patients with normal NCCT or normal neurological examination. Due to the retrospective design of our study we do not know why the treating physician chose to perform these CTAs and more importantly, we cannot determine how many patients did not receive a CTA at all. Second, in some subgroups, such as patients with a normal NCCT, the number of abnormalities was small. Due to the limited number of abnormalities there was insufficient power to determine clinically relevant factors. Alternatively, one could reason that abnormalities in this group are so few that CTA scanning in these patients is not cost-effective. Finally, we had to rely on retrospective chart review and some data, for instance on the presence of nuchal rigidity or evaluation of papillary edema, was missing in a large part of patients, because the performance of such neurological tests may very much depend on the severity of the clinical presentation.

Patients with acute headache and an abnormal NCCT should receive CTA. The yield of CTA in patients with a normal NCCT was low and the number needed to scan to find a clinically relevant abnormality was 27. We feel this may still warrant CTA in this group, particularly if high diagnostic sensitivity is strived for. Clinically relevant diseases such as RVCS or CVT may be missed without additional imaging of the vessels. A prospective study aimed at identifying criteria for selecting patients with a normal NCCT for CTA is therefore needed.

CONFLICT OF INTEREST AND FUNDING

On behalf of all authors, the corresponding author declares no conflicts of interest. No funding was received for the performance of this study.

REFERENCES

1. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *Journal of Neurology Neurosurgery and Psychiatry* 2005;76:1084-1087.
2. Maruyam H, Nagoya H, Kato Y, et al. Spontaneous cervicocephalic arterial dissection with headache and neck pain as the only symptom. *Journal of Headache and Pain*. 2012 13(3):247-253.
3. Mitsias P, Ramadan NM Headache in ischemic cerebrovascular disease. Part I: Clinical features. *Cephalalgia*. 1992; 12:269-274.
4. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm. *Lancet*. 1986 29;2:1247-1248
5. Raps EC, Rogers JD, Galetta SL et al. The clinical spectrum of unruptured intracranial aneurysms. *Archannals of Neurology*; 1993:50:265-268.
6. Witham TF, Kaufmann AM. Unruptured cerebral aneurysm producing a thunderclap headache. *American Journal of Emergency Medicine*. 2000 18:88-90
7. McCarron MO, Choudhari KA. Aneurysmal subarachnoid leak with normal CT and CSF spectrophotometry. *Neurology* 2005 8;64:923.
8. Ducros A. Reversible vasoconstriction syndrome. *Lancet Neurology* 2012; 11: 906–17
9. Cohnen M, Wittsack HJ, Assadi S, et al. Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. *American Journal of Neuroradiology*. 2006; 27:1741-5.
10. R. Dittrich, S. Akdeniz, , S. P. Kloska, et al. Low rate of contrast-induced Nephropathy after CT perfusion and CT angiography in acute stroke patients. *Journal of Neurology* 2007: 1491-1497
11. Luitse MJA, Dauwan M, van Seeters T et al. Acute Nephropathy after Contrast Agent Administration for Computed Tomography Perfusion and Computed Tomography Angiography in Patients with Acute Ischemic Stroke. *International Journal of Stroke*. 2015 10:E35-6.
12. Jamshidi S, Kandiah PA, Singhal AB, et al. Clinical predictors of significant findings on head computed tomographic angiography. *Journal of Emergency Medicine*. 2011;40:469-75.
13. Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. *JAMA*. 2013 25;310:1248-55.
14. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *British Medical Journal.* 2009;338:b604.
15. Greving JP, Schonewille WJ, Wijman CA, Michel P, Kappelle LJ, Algra A; BASICS Study Group.Predicting outcome after acute basilar artery occlusion based on admission characteristics.*Neurology*. 2012 Apr 3;78(14):1058-63
16. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Annals Internal Medicine*. 2015 Jan 6;162(1):55-63.

Chapter 5

OPTIMIZING BLOOD PIGMENT ANALYSIS IN CEREBROSPINAL FLUID FOR THE DIAGNOSIS OF SUBARACHNOID HEMORRHAGE – A PRACTICAL APPROACH

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ABSTRACT

Introduction

Patients presenting with sudden severe headache may have a subarachnoid hemorrhage, (SAH). After a normal head Computer Tomography (CT) a lumbar puncture (LP) is routinely performed to rule out SAH. Photospectrometry is then used to detect bilirubin in cerebrospinal fluid (CSF). Photospectometric analysis of CSF reaches a high sensitivity but a low specificity for SAH. This low specificity necessitates extensive additional research to rule out cerebral aneurysm accompanied by high costs and risk of complications.

Objective

The objective of this study was to retrospectively evaluate two different CSF interpretation methods using photospectrometry in patients presenting with acute headache. The first of these is the Leiden method, an iterative model using a standard calculation. The second is the UK NEQAS guideline, which uses the original spectrum in combination with a decision tree. Our goal was to obtain retrospective data on patients screened with both methods to improve specificity of CSF research.

Results

We included 361 patients in this study, 47 of these had a raised bilirubin concentration in the CSF according to the Leiden method. In only 9 of these 47 patients an aneurysm was found, in the other patients the Leiden test was positive due to other reasons (viral meningitis, hyperbilirubinemia e.a.) Out of the 47 patients with raised bilirubin, 24 could be re-evaluated using the UK NEQAS. Of these 24 patients, 5 had an aneurysm. There were no aneurysms found in patients with a negative result according to the UK NEQAS guideline.

Conclusion

Our data show that a raised bilirubin calculated using the Leiden method seems to have a lower specificity than the UK NEQAS guideline. For practical reasons, it seems advantageous to use the Leiden method as a screening method, and use the UK NEQAS guideline if a positive result is found.

INTRODUCTION

Acute headache is a frequently encountered complaint in the emergency room and can be a presenting sign of subarachnoid haemorrhage (SAH). It is common practice to first perform a Computerized Tomography (CT) of the brain to exclude haemorrhage. The sensitivity of CT is high, almost 100%, in the first 12 hours but this declines to 58% after 5 days [1;2]. In a recent study third generation CT was evaluated with a sensitivity of 100% within the first 6 hours and 85.7% after 6 hours [3]. When there is a high suspicion of SAH it is common practice to subsequently perform a lumbar puncture (LP). Although this practice has been questioned, recent research shows that a LP is still obligatory to exclude an SAH, especially if the patient presents several days after the headache [4;5].

Haemolysis of erythrocytes in the cerebrospinal fluid (CSF) leads to release of oxyhaemoglobin, which is subsequently degraded to bilirubin by the mononuclear phagocyte system. Oxyhaemoglobin (and methaemoglobin) can also be introduced into the CSF by a traumatic puncture and thus may not be conclusive [6]. In contrast, bilirubin levels rise to detectable amounts in the course of approximately 12 hours after an SAH by in vivo conversion of haemoglobin and remains detectable in the CSF for 2-4 weeks after haemorrhage [7]. The presence of the metabolites of erythrocytes in CSF can often be detected by the yellowish appearance of the CSF, called xanthochromia. However, visual inspection of CSF for xanthochromia lacks adequate sensitivity and specificity [8;9;10], so analysis of CSF with UV/VIS-spectrophotometry is often used to qualitively and/or quantitively measure levels of oxy-, methaemoglobin and bilirubin. Currently, in the Netherlands, either an iterative calculation model (Leiden method) [10] or the revised British national guidelines using a decision tree (UK NEQAS guideline) [11] are used to improve the interpretation of the UV/VIS-spectrum of blood pigments in CSF. Sensitivity in CSF-spectrometry methods has been reported to be 100%, however, published specificities of 75 and 83% leave room for improvement [8;12].

The objective of this study was to evaluate and compare the Leiden and UK NEQAS methods in clinical practice and to present an optimal approach for blood pigment analysis to reduce the need for potential hazardous and expensive diagnostic tools such as angiography and contrast MRI.

MATERIALS AND METHODS

Design

Here we describe a retrospective study researching the clinical outcomes of patients presenting in the emergency room from January 2008 through May 2011 with severe, acute, non-traumatic headache, in correspondence to their LP analysis. Patients with pathological findings on standard head CT, such as SAH or subdural hematoma were excluded. If available, neuro-imaging

results of CT-angiogram, angiography and MRI were reviewed. In accordance to the hospital's protocol, LP's were performed at least 12 hours after the onset of symptoms and CSF protein and glucose concentrations were determined. Collected samples were transported to the in-house laboratory constantly shaded from light. Cell-counts for erythrocytes and leucocytes were carried out routinely. The Leiden method was used clinically for CSF analysis. There were no specific ethical concerns or need for informed consent as patients were examined and treated according to current clinical practice.

Assays

Automated assays

Total protein in CSF was measured turbidimetrically after the addition of benzethoniumchloride. Glucose in CSF was determined with the hexokinase-method. Plasma total bilirubin was measured photometrically after reacting with diazonium. All automated assays were performed on a Modular analyser (Roche, Almere, The Netherlands).

CSF sample handling and UV-spectrum measurement

CSF samples obtained from the LP were directly taken to the in-house clinical laboratory. The least blood-stained specimens were used for analysis. After a visual inspection and cell-count, samples were centrifuged for 5 minutes at 1250 g, within 1 hour after LP. Then 100 µl of 0.25 M phosphate buffer pH 6.6 was added to 900 µl of CSF to rule out pH-influences on the UV-absorption characteristics [10]. The sample was transferred into a cuvette with a 1 cm path length. Subsequently, absorbance spectra were made from 350 to 700 nm on a Thermo Evolution 300 using Thermo Vision software (Thermo Scientific, Breda, The Netherlands) using demineralised water as a blank reference.

Interpretation methods

Iterative calculation model ('Leiden method')

To calculate the concentrations of methemoglobin, oxyhemoglobin and bilirubin using an iterative model the method described by Duiser et al. [10] was used. This method requires the Duisersoft Microsoft Excell program (obtained from dr. Duiser). The absorption values at 360, 405, 414 and 455 nm were transferred into this program, which instantly produces a model-spectrum and calculates the concentrations of the various blood pigments. As recommended, bilirubin CSF concentration > 0.2 µmol/L were considered higher than the upper reference value [12] indicating the possibility of an SAH. Values ≤ 0.2 µmol/L were interpreted as 'negative'.

Net bilirubin absorbance ('UK NEQAS guideline')

As an alternative to the iterative model, the spectra of the 118 most recent specimens were also retrospectively interpreted according to the revised UK NEQAS guideline [12]. In contrast to the guideline, the samples were diluted to a small extent due to the addition of the phosphate buffer used in the Leiden method. However, the implications for a correct estimation of the net bilirubin absorbance (NBA) were considered insignificant since the dilution was minimal

and equally present in all samples. A predicted baseline was drawn in the original spectrum and the NBA was measured at 476 nm. At the same time, the net oxyhemoglobin absorbance (NOA) was determined using the predicted baseline and the absorbance maximum between 410-418 nm. Subsequently, the interpretation of the specimens was done using the decision tree as described in the guideline, taking into account the NBA, NOA and serum bilirubin and CSF total protein concentrations. Interpretations were categorized into: 'inconclusive' (due to high NOA), 'no evidence to support SAH', 'consistent with SAH' and 'interpret with caution' (due to CSF protein ≥1.0 g/L).

Patient diagnosis

All digital patient files were searched retrospectively to determine clinical diagnosis. When performed, Computer Tomography Angiogram (CT-A), Magnetic Resonance Imaging (MRI) and Angiography (DSA) were reviewed to establish their contribution to the diagnosis. At least four months after the inclusion patient statuses were revised for missed SAHs or altered diagnosis.

RESULTS

Between January 2008 and May 2011 the CSFs of 361 patients presenting with acute headache were analysed for blood pigments. This cohort was comprised of 234 women (64.5 %) and 127 men, with a mean age of 43.5 years. According to our hospital protocol CSF samples were originally evaluated with the Leiden method. Of all patients included in the study, 47 had a bilirubin concentration of 0.3 µmol/L or higher (13%) in their CSF and 314 were 'negative' according to the Leiden method. Of the 47 patients found to be 'positive', 25 received a CT angiogram, which lead tot the diagnosis of aneurysm in seven patients and sinus thrombosis in two patients The lowest CSF bilirubin concentration in a patient with a confirmed SAH was 0.3 µmol/L. 15 CT angiograms were normal, although two patients with a normal CT angiogram were later diagnosed with an aneurysm after MRI and angiography. Three more patients had an MRI, of which one was normal, one showed hydrocephalus and one showed a sinus thrombosis. Of the 19 patients with a positive bilirubin who did not get a CT angiogram or MRI, six had a viral meningitis, one had had a traumatic LP three days prior showing 1030 erytrocytes and a normal bilirubin count, one had hyperbilirubinemia and 11 did not receive additional neuro-imaging. According to digital patient files after 4 months follow-up none of our patients with a negative CSF result has had a SAH. We cannot however exclude the possibility that patients might have been seen in another neurosurgical centre. The reason for lack of further diagnostics in these cases could not be determined, but in most cases was likely due to low clinical suspicion of SAH.

Of all 361 patients 117 could be re-evaluated using the UK NEQAS guideline. Seven patients were 'consistent with SAH' (6%), 99 spectra were interpreted as 'no evidence to support SAH'. Three patients had an incorrect spectrum recording and one had an inconclusive spectrum due to a severe traumatic puncture. Seven patients were classified as 'interpret with caution' due to

high CSF protein concentrations (>1 g/l). The high protein concentrations could be attributed to (bacterial) meningitis (five patients) and severe traumatic punctures (two patients with erythrocyte counts >100000).

Of the 47 patients that were considered 'positive' according to the Leiden method it was possible to re-evaluate 23 with the UK NEQAS guideline. Six of these patients were also positive using the UK NEQAS guideline (Tabel 1).

Of these 'double positive' patients one did not receive a CT angiogram, but of the other five that did, four had an aneurysm on the CT angiogram, and one an aneurysm after MRI. All the patients that were negative with the Leiden method were also negative using the UK NEQAS guideline.

There were no patients that were positive with the UK NEQAS guideline that were diagnosed with another underlying disease such as viral meningitis, sinus thrombosis or otherwise. One patient with a 'no evidence to support SAH' result following the UK NEQAS guideline was classified as having an aneurysm, however this aneurysm had already been discovered earlier and had been coiled. This patient presented because of a second episode of acute headache.

DISCUSSION

In this study we set out to compare the UK NEQAS guideline and the Leiden method for the interpretation of blood pigment analysis in CSF in patients with acute headache and a normal CT. Our results show that less patients are considered 'positive' using the UK NEQAS guideline (13% vs. 6%). Confounders in the Leiden method are viral and bacterial meningitis and sinus thrombosis, but incorrect spectrum recordings were recorded. This last confounder can be explained by high baseline levels recorded with the Leiden method, caused by spurious UV-absorption (e.g. non-centrifuged samples) resulting in falsely elevated bilirubin levels in the iterative calculation model. In five patients that were positive with the Leiden method (up to 0.6 µmol/L) the UK NEQAS guideline resulted in a negative result without a clear reason, indicating that the cut-off value of 0.007 AU in the UK NEQAS guideline is more conservative. However, as one patient had a confirmed SAH with a CSF bilirubin concentration of 0.3 µmol/L, a higher cut-off value for the Leiden method does not seem feasible.

In earlier studies a high sensitivity has been reported for both the Leiden method and the UK NEQAS guideline of up to 100% [8;12], but, due to a lack of a gold standard for SAH diagnosis we state that it is impossible to calculate a reliable sensitivity and specificity. A previously published prospective study performed a follow-up after 'normal' CT and CSF results and found no patients with SAH. However, in that study one patient was diagnosed with an aneurysm after a MRI [4]. We find similar results; in our study a SAH was discovered with MRI and angiography in two

Table 1. Overview of patients with a positive Leiden guideline reviewed with UK NEQAS Guideline.

Sex, age (years)	Bilirubin (µmol/l)	UK NEQAS guideline	Erytrocyte count (Cells*10^6/l)	Leucocyte count (Cells*10^6/l)	Protein (g/l)	CT angiogram
F, 58	0.8	Consistent with SAH	10443	16	0.4	Not performed
F, 61	6	Consistent with SAH	17000	21	0.66	Normal
F, 45	4.5	Consistent with SAH	20000	209	0.59	Aneurysm
F, 46	1	Consistent with SAH	191000	296	1.15	Aneurysm
M, 53	0.9	Consistent with SAH	40	12	0.34	Aneurysm
F, 69	0.3	Consistent with SAH	78	10	0.6	Aneurysm
F, 52	0.6	No evidence of SAH	830	2	0.3	Normal
M, 53	0.4	No evidence of SAH	25000	19	1.01	Not performed
M, 51	0.3	No evidence of SAH	61	3	0.36	Not performed
M, 39	0.3	No evidence of SAH	23	2	0.48	Not performed
F, 42	0.3	No evidence of SAH	47000	76	0.92	Normal
F, 23	0.3	No evidence of SAH	14933	2	0.78	Normal
M, 48	0.6	TP >1g/l, caution	113000	0	3.18	Normal
F, 57	0.5	TP >1g/l, caution	118000	56	1.36	Normal
F, 57	0.4	TP >1g/l, caution	13	32	1.2	Normal
M, 19	0.3	TP >1g/l, caution	360	280	1.0	Not performed
F, 38	4.2	TP >1g/l, caution	1348	128	1.41	Normal
M, 84 †	0.9	TP >1g/l, caution	352	3200	4.21	Not performed
F, 54	0.3	TP >1g/l, caution	170	1944	1.67	Not performed
M, 44	0.8	NOA >0.1, inconclusive	435000	180	5.35	Tumor mass
M, 16	0.6	'Wrong spectrum'	8	0	0.3	Normal
M, 32	0.3	'Wrong spectrum'	n.d.	n.d.	0.39	Not performed
F, 47	2.2	'Wrong spectrum'	121	2	1.0	Aneurysm

patients after a normal CT angiography. If we were to calculate the sensitivity of the Leiden method and the UK NEQAS guideline this would amount to 100% for both methods in this series. Specificity of the Leiden method was 89%, while specificity of the UK NEQAS method was 99%.

In our study, we evaluated the use of the Leiden method for primary CSF interpretation and, in case of a 'positive' outcome, the use of the UK NEQAS guideline as a secondary method to optimize specificity. This approach was taken since the UK NEQAS guideline, although it appears to have superior specificity, has some practical disadvantages: interpretation has to be performed by an experienced interpreter and CSF protein and serum bilirubin concentrations are mandatory variables [11]. In addition, the time of onset of the symptoms should be taken into account [11;13] and many other variables such as CSF glucose and leucocyte count, recent traumatic punctures and/or light exposure may, although not incorporated in the UK NEQAS guideline, provide crucial information.The Leiden method, on the other hand, has little inter-person variation and a relatively simple workflow [11]. Our data show that by using the Leiden method as a screening tool about 87% of the patients can be diagnosed as 'no evidence to support SAH' as the UK NEQAS guideline and clinical outcome confirmed all these 'negative' patients. In only 13% of the cases an experienced technician or clinical chemist is required for alternative CSF interpretation using the UK NEQAS guideline. As fast CSF interpretation is highly recommended [11], the workflow we propose has practical benefits, especially during out-of-office hours. Moreover, the increase in specificity following this workflow may, due to the low incidence of SAHs in our population (approx. 3%), lead to a significant reduction in potentially harmful and costly imaging techniques

CONCLUSION

Based upon our retrospective evaluation of two CSF interpretation methods in 361 patients with suspicion of a SAH we propose to first perform the Leiden method and in case of a positive result, use the UK NEQAS guideline as a secondary diagnostic method. Using the workflow we propose optimal specificity is achieved with high practicality for clinical laboratories.

REFERENCES

1. Kassell NF, Torner JC, Haley EC Jr, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73(1):18.
2. van der Wee N, Rinkel GJ, Hasan D, et al. Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? J Neurol Neurosurg Psychiatry. 1995;58(3):357.
3. Sames TA, Storrow AB, Finkelstein JA, Magoon MR Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. Acad Emerg Med. 1996;3(1):16.
4. Perry JJ, Spacek A, Forbes M, et al. Is the Combination of negative computed Tomography result and negative Lumbar puncture result sufficient to rule out subarachnoid hemorrhage?. Ann emerg med 2008 vol51 no 6, 707-713
5. Sidman R, Connolly E, Lemke T Subarachnoid hemorrhage diagnosis: lumbar puncture is still needed when the computed tomography scan is normal.. Acad Emerg Med. 1996;3(9):827.
6. R. Beetham. CSF spectrophotometry for bilirubin – why and how? Scan J Clin Lab Invest 2009 (69), 1-7
7. Fishman R.A. CSF in disease of the nervous system. Philadelphia WB Saunders 1980:323.
8. Wood MJ, Dimeski G, Nowitzke AM CSF spectrophotometry in the diagnosis and exclusion of spontaneous subarachnoid haemorrhage. J Clin Neurosci 2005;12:142–6.
9. Petzold A, Keir A, Sharpe LT Spectrophotometry for xanthochromia. N Engl J Med 2004;351:1695-
10. Hendrik J. Duiser, Freek W.C. Roelandse, et al. Iterative Model for the Calculation of Oxyhemoglobin, Methemoglobin, and Bilirubin in Absorbance Spectra of Cerebrospinal Fluid, Clini Chem 200147, No. 2,
11. Anne Cruickshank, Peter Auld, Robert Beetham, et al. Revised national guidelines for analysis of cerebrospinal fluid for bilirubin in suspected subarachnoid haemorrhage.. Ann Clin Biochem 2008; 45: 238–244.
12. Apperloo JJ, van der Graaf F, Dellemijn PL, et al An improved laboratory protocol to assess subarachnoid haemorrhage in patients with a negative cranial CT scan.. Clin Chem Lab Med 44, 938-48, 2006
13. Raashda A. Sulaiman, Rousseau Gama, Pitfalls in cerebrospinal fluid spectroscopy results for the diagnosis of subarachnoid haemorrhage. Br J neurosurg, December 2010; 24(6):726

Chapter 6

PROCALCITONIN IN CEREBROSPINAL FLUID IN MENINGITIS; A PROSPECTIVE DIAGNOSTIC STUDY

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ABSTRACT

Objectives

Bacterial meningitis is a severe but treatable condition. Clinical symptoms may be ambiguous and current diagnostics lack sensitivity and specificity, complicating diagnosis. Procalcitonin (PCT) is a protein that is elevated in serum in bacterial infection. We aimed to assess the value of PCT in cerebrospinal fluid (CSF) in the diagnosis of bacterial meningitis.

Methods

We included patients with bacterial meningitis, both community acquired and post neurosurgery. We included two comparison groups: patients with viral meningitis and patients who underwent lumbar punctures for non-infectious indications. We calculated mean differences and 95% confidence intervals of procalcitonin in CSF and plasma in patients with and without bacterial meningitis.

Results

Average PCT concentrations in CSF were 0.60 ng/ml (95%CI:0.29-0.92) in the bacterial meningitis group (n=26), 0.81 (95%CI:0.33-1.28) in community-acquired meningitis (n=16) and 0.28 (95%CI:0.10-0.45) in post-neurosurgical meningitis (n=10), 0.10 ng/ml (95%CI 0.08-0.12) in the viral meningitis group (n=14) and 0.08 ng/ml (95%CI:0.06-0.09) in the non-infectious group (n=14). Mean difference of PCT-CSF between patients with community-acquired bacterial meningitis and with viral meningitis was 0.71 ng/ml (95%CI:0.17-1.25) and 0.73 ng/ml (95%CI:0.19-1.27) for community-acquired bacterial meningitis versus the non-infectious group. The median PCT CSF: plasma ratio was 5.18 in post-neurosurgical and 0.18 in community-acquired meningitis (IQR 4.69 vs. 0.28).

Conclusion

Procalcitonin in CSF was significantly higher in patients with bacterial meningitis when compared with patients with viral or no meningitis. PCT in CSF may be a valuable marker in diagnosing bacterial meningitis, and could become especially useful in patients after neurosurgery.

INTRODUCTION

Bacterial meningitis is a life threatening but, treatable condition with high morbidity (20%) and mortality (15%) [1]. The gold standard in diagnosing bacterial meningitis is by demonstrating the presence of bacteria in cerebrospinal fluid (CSF) samples via gram staining or CSF cultures. In the acute setting however, bacterial cultures take too much time to be used in the decision whether or not to start antibacterial treatment. Polynuclear pleiocytosis combined with raised CSF protein and lowered CSF glucose indicate bacterial meningitis, but these findings are not sensitive and may not be present in 12% of patients [2-4]. These parameters are even more unreliable in patients with an extraventricular drain (EVD) after subarachnoid- or intracranial hemorrhage as intrathecal plasma leakage causes raised erythrocytes and leucocytes counts [5]. An additional diagnostic marker to distinguish bacterial meningitis from aseptic, viral or no meningitis would therefore be valuable.

Procalcitonin (PCT) is a protein that can be released by parenchymal cells in the presence of endotoxins or cytokines like interleukin-6 and tumor necrosis factor-α. PCT is raised strongly during bacterial inflammation, but not or only marginally elevated in viral or non-infectious inflammatory reactions [6,7]. Whether it is locally produced in the central nervous system is a matter of debate, but calcitonin messenger RNA has been isolated in hamster brain tissue suggesting this possibility [8]. A recent study showed that procalcitonin is produced by trigeminal glia cells in response to inflammation, making local production in the central nervous system more likely [9].

Availability of the PCT-assay on standard immunochemistry platforms allows turn-around-times within an hour, making the test suitable in an acute setting. PCT has been proven to be valuable in differentiating between bacterial and viral meningitis when determined in serum [10-12]. However, the usefulness of PCT in serum of patients with bacterial meningitis after neuro-surgical intervention is limited [13]. Previous studies of PCT measurement in CSF have shown conflicting outcomes. Two studies showed significantly higher PCT concentrations in CSF in patients with bacterial meningitis compared with tick-borne encephalitis or viral meningitis [14,15]. Others have suggested that the level of PCT in CSF did not differ between bacterial and viral meningitis [16]. Methodological factors may explain these conflicting findings. As the analytical performance of the PCT assay has improved since these studies, renewed investigation is warranted.

The aim of this study is to investigate whether there PCT levels in CSF in patients with bacterial meningitis are elevated and whether this could be a potential marker to differentiate between the presence or absence of bacterial meningitis.

MATERIALS AND METHODS

Patients

From September 2012 to February 2015 we prospectively included adult patients (>18 years) who underwent a lumbar puncture on clinical suspicion of bacterial meningitis. Patients presented either to the emergency room, were admitted or were seen as inpatients in our secondary teaching hospital. We aimed to study consecutive patients, however, a small number of patients were missed when seen during on call hours.

The study protocol was evaluated and approved by the local ethics committee. The ethics committee waived the need for consent to participate as PCT was determined in already available CSF and plasma samples (remnants) and no additional sample volumes were taken for the purpose of this study. Patients were investigated and treated according to current clinical practice and were not personally subjected to additional testing or questionnaires.

We divided patients into three groups depending on the outcome of standard CSF examination. First a bacterial meningitis group, both community acquired (CAM) or after neurosurgical procedure (PNM), second a comparison group with viral meningitis and finally a comparison group who underwent lumbar puncture for non-infectious reasons.

Patients were diagnosed with bacterial meningitis if CSF testing showed polynuclear pleocytosis with leucocyte count >2000x10^6/l CSF leucocytes, raised CSF protein > 2.2 g/l, lowered CSF glucose <1.9 mmol/l or a CSF:plasma glucose ratio <0.23. Positive CSF culture, if available, was used as diagnostic gold standard. These conditions have been proven to be 88-99% accurate individual predictors of bacterial meningitis [2,3]. Our bacterial meningitis group consisted of patients with community acquired meningitis (CAM) and patients with post neuro-surgical intervention meningitis (PNM). The interventions in the PNM group consisted of placement of an EVD or craniotomy. By using the same CSF chemistry criteria for the PNM group we aimed to collect not only a homogenous group with bacterial meningitis but also to exclude patients with aseptic meningitis. Second, we hoped to evaluate the differences in PCT outcome between CAM and PNM groups with similar CSF chemistry.

The first comparison group consisted of patients with viral meningitis. A positive PCR was used as gold standard where available. Patients were diagnosed with viral meningitis if CSF testing showed mononuclear pleocytosis with leucocyte count >5x10^6/l, but normal glucose and possibly raised protein.

The second comparison group consisted of patients free of infection. The selection criteria for this group were that patients were free of fever (T <38◦C) and the indication for the LP was unrelated to excluding infectious disease (eg. hemorrhage in acute headache), additionally

normal plasma C-reactive protein (<5 mg/l), normal CSF leucocyte count (<5x10^6/l) and normal CSF glucose (>1.9 mmol/l) and protein (<2.2 l) were mandatory inclusion criteria for this group.

We collected data on clinical characteristics, such as presence of headache, fever, depressed level of consciousness, nuchal rigidity and whether bacterial cultures were positive and with which pathogen.

Sample handling and assays

Lumbar punctures were performed and plasma was obtained before the start of treatment. PCT was determined from the same CSF that prompted a diagnosis of bacterial meningitis or not. The PCT results were not visible for clinicians during diagnosis or treatment. CSF samples obtained from the lumbar puncture were taken to the in-house clinical laboratory within 20 minutes. The least blood-stained specimens were used for analysis. After a visual inspection and cell-count, samples were centrifuged for 5 minutes at 1250 g, within 1 hour after lumbar puncture. Total protein in CSF was measured turbidimetrically after adding benzethoniumchloride, glucose levels were determined with the hexokinase-method and CRP by immunoturbidimetry. Plasma and CSF procalcitonin were measured with the BRAHMS Elecsys two step-immunoassay. If direct measurement of PCT was not possible samples (CSF and/or plasma) were stored at – 20ºC within 24 hours. The functional sensitivity of the PCT assay was <0.06 ng/ml, with an analytical sensitivity of <0.02 ng/ml. There is a reported variation coefficient of < 10% at a concentration of 0.04 ng/ml in plasma [17]. All automated immunochemistry assays were done on a Modular analyser (Roche, Almere, The Netherlands). Standard CSF chemistry and PCT determination were evaluated by the hospital clinical chemist.

Reported reference plasma PCT concentration in healthy adults is <0.10 ng/ml. Reference values for PCT in CSF are unknown [17]. Plasma PCT was not determined in the two comparison groups.

Statistical analysis

We calculated mean differences in PCT levels between patients with and without bacterial meningitis, as well as accompanying 95% confidence intervals (CI). If the 95% confidence interval for the difference does not contain the value 0, the difference is statistically significant and $p<0.05$. For comparison of PCT in plasma and PCT ratios in CSF versus plasma between groups we used the Mann-Whitney U test because the data of these variables were not normally distributed. For these data we gave medians and interquartile ranges (IQR's). To assess the discriminative property for PCT in CSF we made ROC curves and calculated the area under the curve comparing patient groups with an infection (bacterial meningitis, both CAM and PNM, and viral meningitis) with the patients without an infection.

RESULTS

We included 26 patients with bacterial meningitis; 16 patients with community acquired and 10 patients with bacterial meningitis after neurosurgical intervention. We excluded 4 patients with bacterial meningitis who clinically were treated as such, but did not meet the criteria set in advance for CSF diagnosis. Of the PNM patients four had an EVD and six a craniotomy. There were 13 positive CSF cultures among the 26 patients; three Pneumococcus *pneumonia*, three Staphylococcus *epidermidis*, two Neisseria *meningitides*, one Heamophilus *influenza*, one Escherichia *coli*, one Streptoccus *mitis*, one Streptococcus *pneumoniae* and one Listeria *monocytogenes*. The CSF cultures of the remaining patients were negative. In the comparison groups we included 14 patients with viral meningitis and 14 patients without infection. In patients with viral meningitis PCR was positive for Enterovirus in three cases, Herpes Simplex-2 in one case and Varicella Zoster in the last case. In these groups no patients were excluded. Patient characteristics and results are shown in tables 1 and 2.

The average PCT in CSF in the group of bacterial meningitis patients was 0.61 ng/ml (95%CI 0.27-0.93). The PCT in CSF in the group of patients with bacterial meningitis was significantly higher when compared with viral meningitis and the group without infection PCT in CSF (table 2). PCT in CSF was not significantly different between CAM or PNM patients (mean difference 0.53 ng/ml; 95% CI -0.13-1.19). The PCT in CSF of the PNM patients was significantly higher than the viral meningitis group and the group without infection (figure 1, table 2).

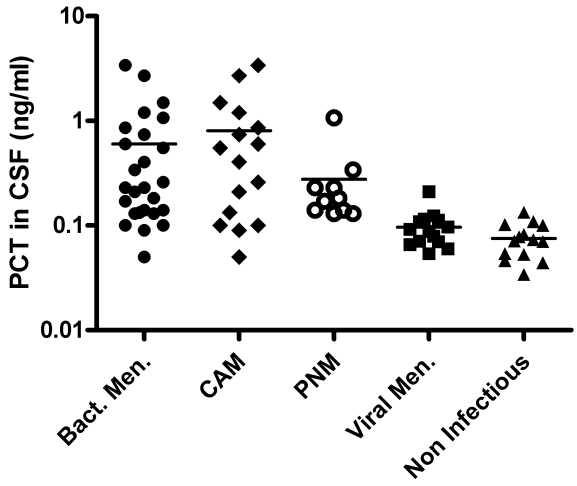

Figure 1. Scatter plots of procalcitonin in cerebrospinal fluid in the studied groups. Horizontal bar represents the mean value of a group, logarithmic scale.

Table 1. Patient characteristics

	Bacterial meningitis Entire group (n=26)	Bacterial CAM (n=16)	Bacterial PNM (n=10)	Viral meningitis (n=14)	Non-infectious (n=14)
Age (years)	62 (SD 16)	60 (SD 18.6)	64 (SD 12)	34 (SD 9)	44 (SD 14)
Range	20-84	20-84	51-83	20-50	22-71
Sex (male)	19 (73%)	12 (75%)	7 (70%)	6 (43%)	4 (29%)
Fever	18 (69%)	12 (75%)	6 (60%)	6 (43%)	0
Ave CRP mg/l (SD)	121 (102)	178 (88)	36 (44)	14 (28)	1.5 (1.2)
Nuchal rigidity	14 (50%)	10 (63%)	4 (40%)	3 (21%)	0
Glascow coma score ave	11	11	12	15	15
Headache	19 (73%)	12 (75%)	7(70%)	14 (100%)	11 (78%)
Culture positive	13 (50%)	10 (63%)	3 (33%)	5 (36%)	0

Legend: CAM community acquired meningitis, PNM post neurosurgical meningitis

Table 2. Results of cell counts, glucose, protein and PCT in CSF and PCT in plasma per group

	Bacterial meningitis (n=26)	CAM (n=16)	PNM (n=10)	Viral meningitis (n=14)	Non-infectious (n=14)
CSF leucocyte count*10^6/l ave	5998	7551	3514	267	1
Polynuclear cells *10^6/l ave	5589	7428	2832	28	0.1
Mononuclear cells*10^6/l ave	616	576	677	239	0.7
Erythrocytes *10^6/l ave	23649	12892	408597	180	287
CSF glucose mmol/l ave	1.6	1.0	2.6	3.5	3.4
CSF protein g/l ave	3.3	3.9	2.4	1	0.4
PCT in CSF ng/ml Average (95% CI)	0.61 (0.29-0.90)	0.81 (0.31-1.31)	0.29 (0.10-0.45)	0.10 (0.08-0.12)	0.08 (0.05-0.09)
PCT in plasma ng/ml Median (IQR)	0.5 (4.36)	1.28 (6.82)	0.05 (0.08)	0.02 (0.02)	-
PCT ratio CSF:plasma Median (IQR)	0.86 (2.79)	0.18 (0.27)	5.18 (4.69)	3.00 (1.38)	-
Mean difference PCT in CSF vs. non infectious (95% CI)	0.74 ng/ml (0.20- 1.28)	0.73 ng/ml (0.20-1.27)	0.21 ng/ml (0.05- 0.37)	0.30 ng/ml (-0.001- 0.05)	-
Mean difference PCT in CSF vs. Viral meningitis (95% CI)	0.73 ng/ml (0.19-1.27)	0.71 ng/ml (0.18-1.25)	0.18 ng/ml (0.02-0.34)	-	-

Legend: CAM community acquired meningitis, PNM post neurosurgical meningitis, CSF cerebrospinal fluid, PCT procalcitonin

The median PCT in plasma of the entire bacterial meningitis group was 0.50 ng/ml (IQR 4.36). The median levels of PCT in plasma showed a statistically significant difference between the bacterial and viral meningitis groups (p=<0.001). The median plasma PCT in the PNM group of 0.05 ng/ml (IQR 0.08) was significantly lower than that in the CAM group of 1.28 ng/ml (IQR 6.82) (p=<0.001) (figure 2). Five out of ten patients (50%) in de PNM group had plasma PCT levels within the reported reference range of <0.1 ng/ml.

The PCT CSF: plasma ratio was significantly higher in PNM patients (median 5.18, IQR 4.69) than in patients with CAM (median 0.18, IQR 0.27) (p<0.001), due to a higher PCT in CSF in comparison with PCT plasma levels in PNM patients (figure 3). We also compared these ratios between patients with low and high erythrocyte counts (< 40 and ≥2000x10^6/l erytrocytes) in order to ascertain whether outcome was influenced by traumatic lumbar puncture both in patients with CAM and PNM. In the CAM group, nine patients had ≥2000x10^6/l erythrocytes in CSF and five CAM patients had an erythrocyte count <40 x10^6/l. The PCT CSF:plasma ratio in these groups was not significantly different (ery's <40 median 0.18, IQR 0.31, ery's >2000 median 0.33, IQR 0.25) (p=1). In PNM eight patients had ≥2000x10^6/l erythrocytes in the CSF. In this group the median PCT CSF: plasma ratio was 5.18 (IQR 3.18). Only one patient had <40x10^6/l erythrocytes in his CSF with a CSF: plasma ratio of 1.6. The final PNM patient had 597x106/l erythrocytes and a PCT CSF:plasma ratio of 9.3.

We also compared PCT levels in patients diagnosed with bacterial meningitis with and without positive bacterial CSF cultures. The average PCT in CSF of patients with a positive culture was 0.82 ng/ml (SD 1.03, N=13). The average PCT in CSF of patients with a negative culture was

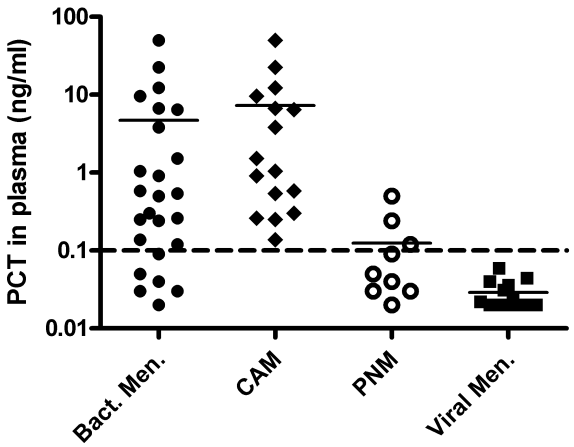

Figure 2. Scatter plots of procalcitonin in plasma in the studied groups. Horizontal bar represents the mean value of a group, logarithmic scale. The dotted line represents procalcitonin normal value in plasma.

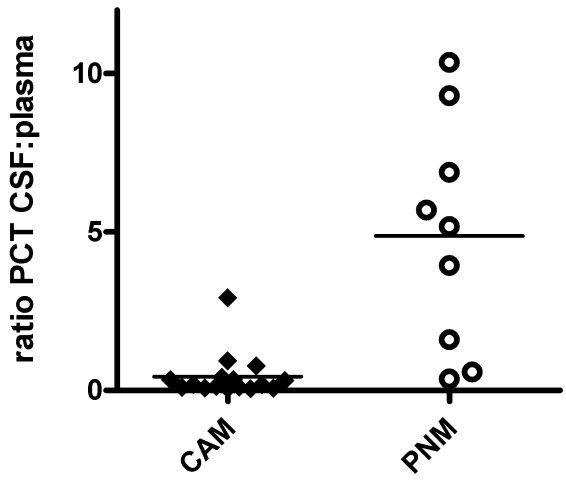

Figure 3. Scatter plots of procalcitonin plasma:CSF ratio. Horizontal bar represents the mean value of a group, logarithmic scale.

0.41 ng/ml (SD 0.35, N=13). The difference between these levels was not statistically significant (mean difference 0.41 ng/ml; 95% CI -0.18-1.00).In the PNM group four patients received an external ventricular drain and six underwent a craniotomy. Statistical analysis showed no effect of type of neurological surgery on PCT values (mean difference 0.06; 95%CI:-0.39-0.51). PCT in plasma was not significantly lower in patients after EVD than in patients after craniotomy (mean difference 0.16; 95%CI:-0.06-0.38). However the confidence interval is wide due to the small patient subgroup. In PNM three CSF cultures were positive which were all found in the craniotomy group.

The receiver-operator curve (ROC) for PCT in CSF of patients with bacterial meningitis versus the patients without an infection had an area under the curve (AUC) of 0.93 (95% CI 0.86-1.00). The AUC of the ROC for the CAM vs. the group of patients without an infection was 0.90 (95% CI 0.78-1.00) and PNM vs. group of patients without an infection was 0.99 (95%CI 0.96-1.00). The AUC of the ROC for viral meningitis vs. the group of patients without an infection was 0.67 (95% CI 0.47-0.87) (figure 4).

In order to be able to calculate sensitivity specificity and positive and predictive value, we chose a cut off value for PCT in CSF based on our reference groups. We arbitrarily chose a cutoff value for PCT in CSF of >0.9 ng/ml. This is the upper limit of the 95% CI of PCT in CSF in the non-infectious group. With this cutoff value we found a sensitivity of 92% (95% CI 75-99%) and a specificity of 68% (95% CI 48-84%). Positive predictive value is 73% (95% CI 55-87%) and negative predictive value is 90% (95% CI 70-99%).

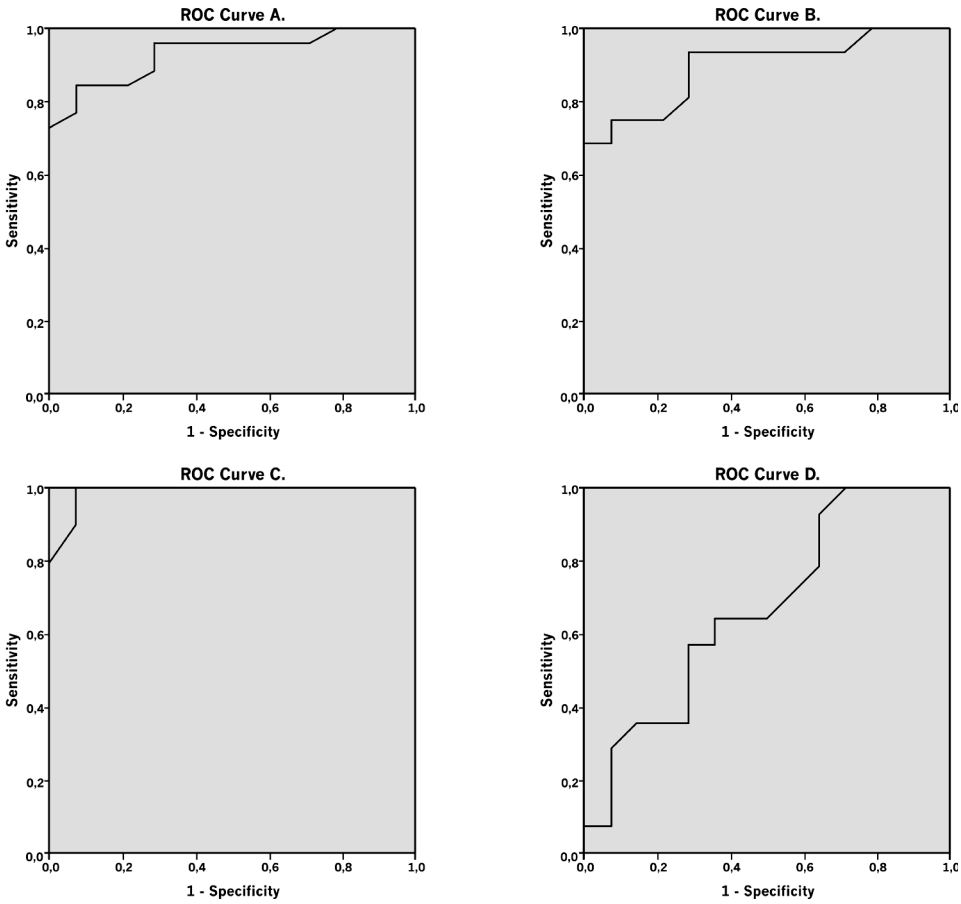

Figure 4. ROC curves for PCT in CSF compared to non-infectious patients for A: all bacterial meningitis patients, area under the curve (AUC) 0.93, B: community acquired meningitis. AUC 0.90, C: post neurosurgical meningitis, AUC 0.98, D: viral *meningitis, AUC 0.67.*

DISCUSSION

Our results show that in our patient population PCT in CSF is significantly higher in patients with bacterial meningitis when compared to patients from the two comparison groups: viral meningitis and the group of patients without an infection. This counts for patients with community acquired meningitis as well as patients with meningitis after a neurosurgical procedure.

PCT in plasma of patients with bacterial meningitis was significantly higher than that of patients with viral meningitis. But PCT in plasma of the PNM group was not significantly higher than in the viral meningitis comparison group. For this subgroup PCT in plasma seems less sensitive than

PCT in CSF. This finding corresponds with an earlier study that evaluated the use of PCT in serum of post-neurosurgical patients and found that in serum sensitivity of PCT is low for diagnosing bacterial meningitis [13].

The findings above raise the question whether there is intrathecal production of PCT. Due to its large molecular structure (13kDa) and being a protein, it is unlikely that PCT passes the blood brain barrier in healthy adults [18]. However, in meningitis the blood brain barrier may be compromised due to infectious processes. Similarly, traumatic lumbar puncture may confound results by plasma leakage. Most of our bacterial meningitis samples had high erythrocyte counts (see table 2). However, when patients with low or high erythrocyte counts with CAM and PNM were grouped and compared, PCT ratios were the same irrespective of erythrocyte count. This makes it highly unlikely that the elevated PCT in CSF originates from leakage of PCT plasma through the blood brain barrier or traumatic lumbar puncture.

Strikingly, the CSF:plasma ratio of PCT was significantly higher in the PNM group compared with the CAM patients. This indicates a much stronger increase of PCT in CSF than in plasma in the PNM group. Moreover, most plasma PCT levels in the PNM group were within the reported reference range of < 0.10ng/ml. We hypothesize this skewed distribution in favor of PCT in CSF in the PNM group may be due to a direct bacterial port of entry after neuro-surgery and the lower level of systemic infection in these patients. We surmise PCT levels may only become raised in blood if bacterial meningitis is accompanied by systemic infection or sepsis, as is the case in most CAM patients. For patients with PNM determining PCT in CSF may become useful as a diagnostic marker.

Our study has limitations. First, study size is relatively small, limiting the power of the study. However, despite the small number of patients we still found a significant difference between groups, with confidence intervals that are sufficiently narrow to allow precise determination of between group differences. Second, we could not prove the presence of meningitis in all patients by means of a positive CSF culture, resulting in potential bias due to miss-classification. Since only 44% of patients have all characteristics of bacterial meningitis [2] we may have included patients in the wrong group. To diminish this possibly important methodological shortcoming we used international CSF diagnostic values which are individual positive predictors in 88-99% [2,3]. In choosing these parameters we also hoped to bypass the chance of diagnosing aseptic meningitis as bacterial meningitis. The downside of using these set parameters was that we could not calculate the added value of PCT against the conventional diagnostic markers. The calculation of an ROC curve of PCT in CSF vs. leucocyte count for instance was not possible.

We calculated whether there was a difference in PCT levels in CSF in patients diagnosed with bacterial meningitis with a positive and negative bacterial CSF culture and found that the difference is not statistically significant. This supports our correct selection of patients for the bacterial meningitis group based on CSF chemistry.

Finally, there are no reference values for PCT in CSF available. By including a group with major headache as complaint and no CSF abnormalities we aimed to include a 'best-available' reference group for CSF PCT. We arbitrarily determined a theoretical reference value based on the upper limit of the 95% CI of PCT in CSF for the non-infectious group. With this value we calculated sensitivity, specificity, negative predictive and positive predictive value for PCT in CST. These results show a good sensitivity and negative predictive value, but need to been seen only as a measure for easier interpretation of the outcomes; they cannot be extrapolated for clinical use. Future research will be needed to determine validated reference values.

As we have measured PCT in CSF at one point in time only, we do not know at what moment after infection peak levels are reached or when PCT levels start to decrease again. This is a highly interesting and clinically relevant issue and we are presently performing a follow-up study in which daily PCT levels are measured in patients with an external ventricular drain.

Our results show that PCT in CSF could become a useful marker in diagnosing bacterial meningitis. This may in particular be the case in patients with suspected meningitis after neurosurgical intervention (in contrast to plasma PCT). However, as the PNM group was limited this conclusion must be tentative. To our knowledge this is the first article including results of procalcitonin both in plasma and in CSF in a varied range of patients groups. An evaluation of PCT CSF:plasma ratios in patients with bacterial meningitis has not been done before. A recent study confirmed our results in CSF, but plasma levels were not included and therefore a direct comparison of PCT in CSF and plasma was lacking [15]. The use of PCT in CSF in determining the need for and possibly duration of antibiotic treatment was beyond the scope of this study, but we hope our data will open the path to research in that direction. Further research on this subject is needed to assess the usefulness of this marker in clinical practice.

We found that PCT is significantly raised in CSF in patients with bacterial meningitis when compared to patients with viral or no meningitis. PCT in CSF may become a useful biomarker in this patient group and especially in patient after neuro-surgery.

REFERENCES

1. Gans de J, D van de Beek. European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis: N Engl J M. 20:1549-56, 2002
2. Beek van de D, Drake JM, Tunkel AR: Nosocomial bacterial meningitis. N Engl J M. 362:146-54, 2010
3. Beek van de D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M: Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J M. 351:1849-1859, 2004
4. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, et al: Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J M. 328:21-8, 1993
5. Schinkel J, Roelandse FW, Geskus RB, Visser LG, van Dijk JM, Voormolen JH, et al: Lack of value of routine analysis of cerebrospinal fluid for prediction and diagnosis of external drainage-related bacterial meningitis. J Neurosurg. 104:101-8, 2006
6. Karzai W, Oberhoffer M, Meier-Hellman A, Reinhart K: Procalcitonin - a new indicator of the systemic response to severe infection. Infection. 25:329–334, 1997
7. Meisner M (ed): Procalcitonin (PCT). A new, innovative infection parameter. Biochemical and clinical aspects. B.R.A.H.M.S. Diagnostica GmbH. ISBN: 3-13-105503-0.Thieme, Stuttgart, New York 2000
8. Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF: Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab. 86:396-404, 2001
9. Raddant AC, Russo AF. Reactive oxygen species induce procalcitonin expression in trigeminal ganglia glia. Headache. 2014 54:472-84.
10. Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al: Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: a European multicenter case cohort study. Arch Pediatr Adolesc Med. 162:1157-63, 2008
11. Gendrel D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, et al: Measurement of procalcitonin levels in children with bacterial or viral meningitis. Clin Infect Dis. 24:1240–1242, 1997
12. Viallon A, Desseigne N, Marjollet O, Birynczyk A, Belin M, Guyomarch S, et al: Meningitis in adult patients with a negative direct cerebrospinal fluid examination: value of cytochemical markers for differential diagnosis. Crit Care. 15:R136, 2011
13. Choi SH, Choi SH: Predictive performance of serum procalcitonin for the diagnosis of bacterial meningitis after neurosurgery. Infect Chemother. 45:308-14, 2013
14. Jereb M, Muzlovic I, Hojker S, Strle F: Predictive value of serum and cerebrospinal fluid procalcitonin levels for the diagnosis of bacterial meningitis. Infection. 29:209-12, 2001
15. Konstantinidis T, Cassimos D, Gioka T, Tsigalou C, Parasidis T, Alexandropoulou I, et al: Can procalcitonin in cerebrospinal fluid be a diagnostic tool for meningitis? J Clin Lab Anal. 2014 ePub ahead of print; DOI 10.1002/jcla.21746.
16. Shimetani N, Shimetani K, Mori M: Levels of three inflammation markers, C-reactive protein, serum amyloid A protein and procalcitonin, in the serum and cerebrospinal fluid of patients with meningitis. Scand J Clin Lab Invest 61:567-74, 2001

17. Lloyd MM, JM Kuyl. Comparison of three methods for procalcitonin analysis: Medical Technology SA. 26:48-52, 2012

18. Maruna P, Nedelníková K, Gürlich R: Physiology and genetics of procalcitonin. Physiological Research. 49 Suppl 1:S57-61. 2000

Chapter 7

D-DIMER FOR THE EXCLUSION OF CEREBRAL VENOUS THROMBOSIS: A META-ANALYSIS OF LOW RISK PATIENTS WITH ISOLATED HEADACHE

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ABSTRACT

Background

Patients with isolated headache may have cerebral venous thrombosis (CVT). D-dimers are proven sensitive in excluding deep venous thrombosis (DVT) and pulmonary embolism (PE) in low risk patients. We aimed to determine whether D-dimer may play the same role in low risk CVT patients with isolated headache.

Methods

We included consecutive patients suspected of CVT from our teaching hospital with isolated headache, a normal neurological examination and normal standard head CT in whom D-dimer was determined. Additionally we did a systematic review on articles describing consecutive patients suspected of CVT with isolated headache and their D-dimer values. CVT was investigated with CT or MR venography in all patients.

Results

A total of 636 consecutive patients were collected from our own data and the literature search. Of 45 CVT patients one had a negative D-dimer (7.5%). Sensitivity of D-dimer for diagnosing CVT was 97.8% (95%CI: 88.2%-99.6%), specificity was 84.9% (95%CI: 81.8%-87.7%), positive predictive value was 33.1% (95%CI: 25.2%- 41.7%), negative predictive value was 99.8% (95%CI: 98.9%-100%). Another 56 isolated headache CVT patients were identified in literature, lacking consecutive isolated headache controls. Sensitivity of D-dimer for diagnosing CVT including these patients was 87.1% (95%CI: 79.0%-93.0%).

Conclusions

D-dimers have a high negative predictive value in patients with isolated headache for excluding CVT. Sensitivity is lower but comparable to the values accepted in PE and DVT. D-dimers in combination with a normal neurological examination and normal standard CT may reduce unnecessary imaging, making it a potentially valuable marker in low risk patients.

BACKGROUND

Headache frequently leads to emergency room consultation. It is vital to exclude secondary forms of headache requiring further treatment such as cerebral venous thrombosis (CVT). CVT is accompanied by headache in 89% of cases [1,2]. It may present with headache alone in 14% [3] and acute headache in 3-13% of cases [4-6]. Patients with isolated headache seem to have a good prognosis, however, CVT patients with isolated headache who present early (<7 days) are more at risk to deteriorate neurologically than patients with isolated headache who present later, making diagnosis in an early stage important [6].

D-dimers have been proven useful in the diagnosis of pulmonary embolism (PE) and deep venous thrombosis (DVT) [7,8]. Clinical factors are translated to the Wells score, ranking patients to high or low risk categories [7]. The Wells score for PE is calculated based on clinical parameters and patient history. The score includes clinical signs of DVT, PE being the most likely diagnosis, heart rate over 100bpm, recent immobility or surgery, hemoptysis, previous PE or DVT or the presence of malignancy , Each item in the Wells score has a rating and patients with 1.5 point or less are rated low risk for PE. When low risk Wells score patients have a normal D-dimer, the post-test probability of DVT or PE is 0.5-2% when using a sensitive ELISA quantative assay [9]. In these low risk patients it is safe to forego further imaging such as echo venography of the lower limbs or pulmonary spiral CT. Sensitivity of D-dimer varies from 83-96% in diagnosing DVT patients and 75-97% in diagnosing PE patients, depending on the performed D-dimer test [10].

Whether the measurement of D-dimer can play a similar role in suspected cerebral vein thrombosis remains uncertain. A recent meta-analysis of the literature concluded that D-dimer may be useful as a diagnostic tool in CVT patients in general, but an analysis for isolated headache was not the aim of this review [11]. According to American guidelines patients with a high clinical suspicion of CVT should receive neuro-imaging regardless of D-dimer results [12]. This makes D-dimer a superfluous test in high risk cases. The definition of low risk patients for CVT requires different criteria from the Wells score for PE of DVT. In current practice the presence of neurological deficit and abnormalities on standard head CT, but also known risk factors for CVT such as pregnancy or use of oral contraceptives are weighed in the decision to perform further diagnostic work-up. Whether D-dimers are sensitive enough to exclude CVT in low risk patients, without these characteristics and isolated headache is unknown. In these patients D-dimer would be valuable to decide whether or not additional imaging is necessary. 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 [13]. Another prospective study found no false negative D-dimers in 20 patients with isolated headache [14].

We aimed to assess whether D-dimer is a valuable test in CVT patients with isolated headache and a low risk of CVT.

METHODS

Patient study

We retrospectively included all consecutive patients with headache who presented to the emergency room of our large teaching hospital from January 2010 to December 2014 with headache if a D-dimer was determined at presentation and the presence of CVT was examined with CT venography or MRI or both. D-dimers were determined routinely by the treating physician when CVT was suspected. As this study was done retrospectively reviewing patient charts, formal approval of the local ethics committee was not applicable. We defined isolated headache as headache in the absence of abnormalities at neurological examination: lowered consciousness, seizures, focal motor deficit, focal sensory deficit, visual field defects, abnormal pupillary responses, eye movement disorders, papillary edema and pathological tendon or plantar reflexes. We only included patients with normal standard head CT. We felt that in the presence of hemorrhage or other abnormalities suspected for CVT at standard CT, follow up diagnostics would have been done regardless of D-dimer values. We included patients with known risk factors for CVT including oral contraceptive use, pregnancy or in puerperium.

We recorded headache characteristics including duration and onset, the presence of nausea and vomiting and also the number of affected sinuses. Also diagnoses at presentation and after 1 year of follow-up were recorded.

D-dimer was determined by the in house laboratory with a Roche second generation latex essay, turbidimetric method on a modular chemistry analyzer. D-dimer was deemed negative if lower than 0.5 µg/ml. We adopted this cut-off value for CVT also as data differently to this are lacking.

Patients underwent scanning by GE Lightspeed 64 slice CT scanner using intravascular iodine contrast. The CT angiography depicted both the arterial and venous system of intra- and extracranial vessels, by scanning the early and late phase of contrast passage. MRA was done with a 1.5 Tesla Siemens MRI with gadolinium enhanced venography or Time of Flight (TOF) imaging.

Literature search

Literature search for articles was done in Pubmed, and Embase with the following search criteria: “cerebral venous thrombosis”, “cerebral venous sinus thrombosis”, “Ddimer”, “D-dimer”, “isolated headache” and combinations of these. We also scanned reference lists of found articles for possible inclusions. We included original articles focusing on D-dimer determination in consecutive patients with suspected CVT, where the presence of isolated headache could be determined. Articles were excluded for the meta-analysis if they were reviews or comments. Articles were scanned for information on patients with isolated headache. If insufficient data were given in the articles, authors were approached for unpublished data on these patients. We evaluated the articles with the QUADAS-2 checklist, which is recommended to evaluate the risk of bias and applicability of primary diagnostic accuracy studies. [15]

In these articles data on duration of complaints, risk factors for CVT and headache characteristics were also recorded.

Data analysis

Data were evaluated with 2x2 contingency tables and we calculated 95% confidence intervals for proportions. Sensitivity, specificity and the negative and positive predictive value could be calculated for both our own data and the data extracted from the systematic review. An additional calculation of sensitivity was done including patients from literature with established CVT that either lacked isolated headache controls or with insufficient information on the control group given in the article. As a matched control group was not present for these patients it was not possible to calculate specificity, negative predictive value or positive predictive value for this entire group.

RESULTS

Patient study

In our center we found 672 patients who presented to the emergency room with headache in whom D-dimer was determined. Of these patients 312 received sufficient imaging to investigate the presence of CVT and 149 of these (47.7%) had a normal neurological examination and normal standard head CT. Neuro-imaging in these patients consisted of CTA/V in 105, MRI in 23 and both modalities in 18 patients (table 1). Average age was 42 years and there were 42 men (28%). Three patients had CVT (2.7%) and all had a raised D-dimer. Of the 146 patients without CVT, 63 had a raised D-dimer. Sensitivity was 100% (95% CI: 30.5- 100%), specificity 56.8% (95% CI: 48.4-65.0%), positive predictive value was 4.55% (95% CI: 1.00-12.7%) and negative predictive value 100% (95% CI: 95.6-100%). Average time between symptom onset and diagnosis was 11 days (SD 16) in the CVT group and 16 days (SD 88) in the non CVT group. Two patients were pregnant and eight had a known use of oral contraceptives. Two patients using oral contraceptives had CVT and both had a raised D-dimer.

Literature search

We identified 118 potentially relevant articles. After excluding duplicates, scanning of titles and abstracts 17 articles remained (see figure 1). After further evaluation of these articles we found eight articles that described both CVT and non CVT groups with isolated headache and their D-dimer levels (table 2). Full information could be immediately extracted from two articles [14,16]. In total six authors were approached for additional information. We received additional information from one of the approached authors adding information on 173 patients [17]. Characteristics of the included articles were evaluated with the QUADAS-2 (figure 2).

We included 487 patients from the three articles with complete information [14,16,17]. Of these patients 42 had CVT (8.6%) of whom one (2.4%) had a negative D-dimer. One patient was

Table 1. Characteristics of included patients from our hospital

	CVT +	CVT -	Total
Patients	3	146	149
Age (mean)	35	42	42
Men (%)	3 (100%)	39 (27%)	42 (28%)
Side of headache			
Bilateral	3 (100%)	105 (71.9%)	108 (72.5%)
Unilateral	0	36 (24.7%)	36 (24.1%)
Local(eye)	0	5 (3.4%)	5 (3.4%)
Acute onset of headache	0	62 (41.6%)	62 (41.6%)
Days to presentation median (IQR)	2 (0-8)	3 (1-7)	3 (1-7)
Nausea	3 (100%)	81 (55.5%)	84 (56.4%)
Vomiting	3 (100%)	51 (34.9%)	54 (36.2%)
CTA/V	0	105 (72%)	105 (70.5%)
MRA/V	0	23 (16%)	23 (15.5%)
Both CTA/V en MRA/V	3 (100%)	18 (12%)	21 (14%)
Raised D-dimer	3 (100%)	63 (43%)	66 (44%)
Diagnosis			
Tension type headache		81	
Migraine		24	
Para Infectious		8	
Paroxysmal hemicrania		4	
SAH		5	
IIH		2	
Other		22	

Legend: CTA CT angiography, CTV CT venography, MRA MR angiography, SAH Subarachnoid hemorrhage, IIH idiopathic intracranial hypertension

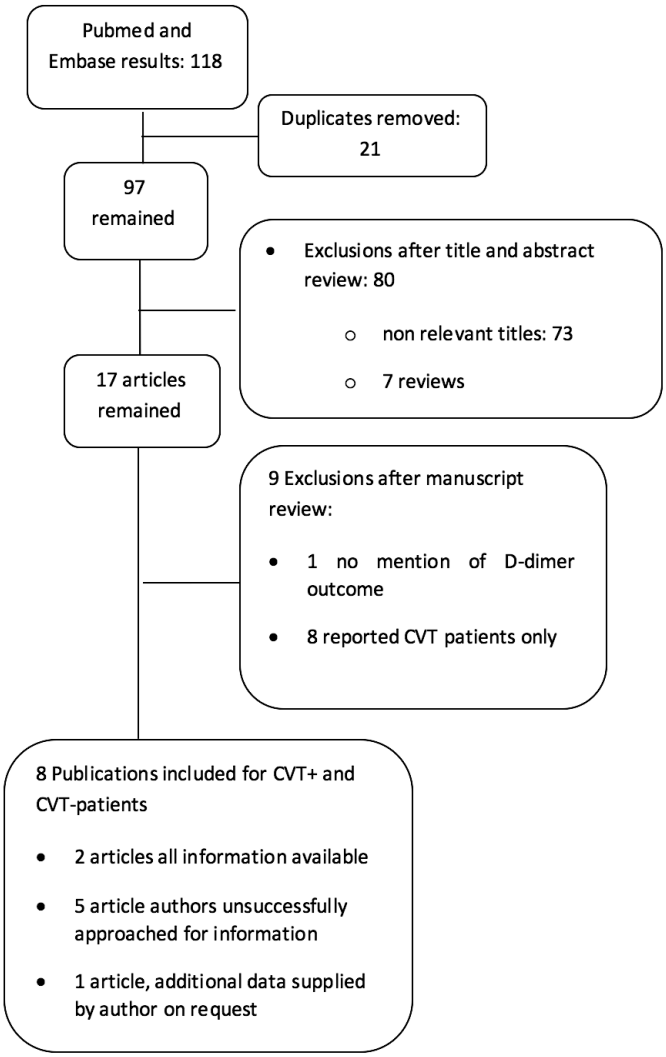

Figure 1. Literature search results for articles on patients with isolated headache, with and without CVT and D-dimer determination.

Table 2. Study characteristics of studies describing consecutive patients suspected of CVT.

	Study design	All/ isolated headache patients	D-dimer test	cut-off value	Imaging	Missing information
Tardy et al [16]	Prospective	52/23	ELISA Vidas assay	>0.5 µg/ml	MRA	None missing
Kosinski, et al [14]	Prospective	343/291	2nd generation latexagglutination	>0.5 µg/ml	MRA or CTV	None missing
Meng, et al. [17]	Prospective	233/173	Immuno- turbidimetric assay	>0.5	MRI/MRV	None missing
Tanislav et al. [18]	Retrospective	239/X	Turbidimetric	>0.19 µg/ml	CTV or MRV	Isolated headache unclear
Ghaffarpour et al. [24]	Prospective	104/X	Conventional ELISA	>0.5 **µg/ml**		Isolated headache unclear
Gouda, Sabry [20]	Prospective	104/X	2nd generation latexagglutination	>0.5 µg/ml	TOF MRA	isolated headache unclear in non CVT group
Lalive, et al [19]	Prospective	54/X	ELISA Vidas assay	>0.5 µg/ml	MRA	Isolated headache unclear in non CVT group
Cucchiara, et al [21]	Prospective	31/X	ELISA Vidas assay	>0.5 µg/ml	MRV	Isolated headache unclear in non CVT group

Legend: MRA MR angiography, MRV MR venography, CTV CT venography, TOF time of flight, CVT cerebral venous thrombosis

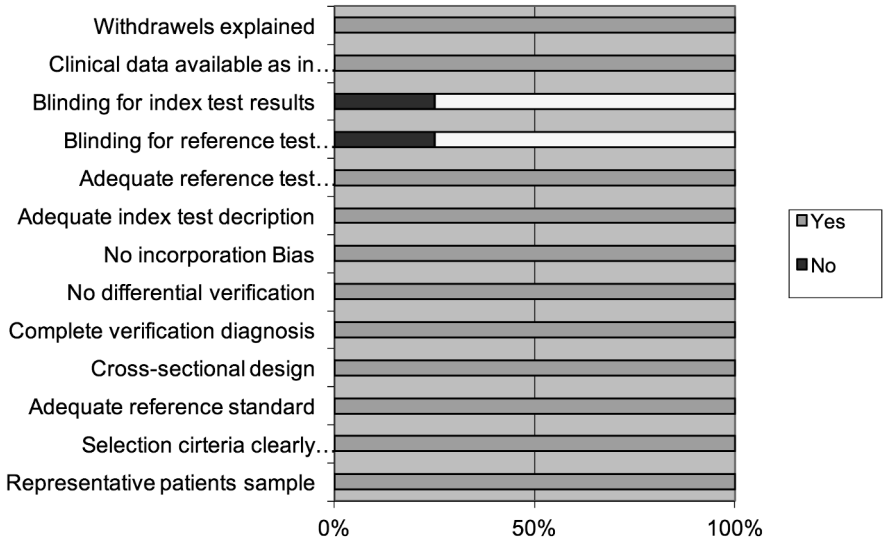

Figure 2. QUADAS-2 Checklist of three included articles and own methods

pregnant and 14 used oral contraceptives. This information was only given for patients with established CVT. All patients with these risk factors had a positive D-dimer. There were 445 patients without CVT, of whom 416 had a negative D-dimer.

Combined data

We included 636 consecutive patients with suspected CVT and normal neurological examination from both our data and the collected articles (table 3). In this group 45 had CVT (7.1%) of whom 1 had a negative D-dimer (1.6%). Sensitivity was 97.8% (95% CI: 88.2%-99.6%), specificity was 84.9 % (95% CI: 81.8%-87.7%), positive predictive value was 33.1% (95% CI: 25.2%- 41.7%), negative predictive value was 99.8% (95% CI: 98.9%-100%) (figure 3). After D-dimer determination there is a 0.2% chance of CVT in patients with isolated headache and a negative D-dimer. The prevalence of CVT in this group with isolated headache was 7.5%. There is a 6.9% post-test reduction of the chance of having CVT in patients with normal neurological examination after D-dimer determination.

We also evaluated the articles that included only patients with established CVT [13, 22,23] and articles with insufficient data on non-CVT patients [19-21]. From these articles we included another 56 CVT patients (table 4). Of the combined 101 patients with CVT and isolated headache 13 (12.9%) had a false negative D-dimer. D-dimer in this group had a sensitivity of 87.1% (95% CI: 79.0%-93.0%).

Table 3. Data on 636 patients with isolated headache

	CVT		No CVT	
	D-dimer raised	D-dimer normal	D-dimer raised	D-dimer normal
Tardy et al, 2002	6	0	0	17
Kosinski et al, 2004	20	0	27	244
Meng et al. 2014	15	1	2	155
Alons et al, 2015	3	0	63	83
Total	44	1	92	499

Table 4. D-dimer results of CVT patients from articles describing established CVT patients with insufficient data on isolated headache in non CVT group.

	D-dimer raised	D-dimer normal	Total (% D-dimer -)
Misra et al, 2009	2	1	3 (33%)
Hiltunen et al, 2013	17	2	19 (10%)
Crassard et al., 2005	14	5	19 (26%)
Gouda, Sabry, 2010	3	3	6 (50%)
Lalive et al, 2003	5	1	6 (17%)
Cucchiara et al, 2005	3	0	3 (0%)
Total	44	12	56 (27%)

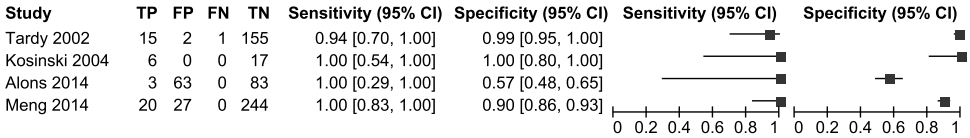

Figure 3. Overview of the sensitivity and specificity of the included articles

In only 33 of the 101 CVT patients information on sinus involvement was available [13,16,19-22]. Of these patients 13 had a single affected sinus and D-dimer was negative in 7 cases (54%). In 11 patients with 2 affected sinuses D-dimer was negative in 4 (36%). In 9 patients with three or more affected sinuses none of D-dimers were negative (0%). Information on duration of symptoms was available for 42 of 101 CVT patients [16-21]. Seventeen patients had complaints <7 days and 6 (35%) of these patients had negative D-dimer. Of the 18 Patients with headache >7 days 5 (28%) had negative D-dimer. Of the seven patients with headache >14 days 3 (43%) had negative D-dimer.

Of the 25 patients who were either pregnant, in puerperium or using oral contraceptives, 17 had CVT and none had a false negative D-dimer. However data on these risk factors for non-CVT controls were not given or could not be reliably deduced in the patients from literature.

DISCUSSION

Our study suggests that D-dimer is a sensitive diagnostic tool in excluding CVT in low risk patients. We found a high negative predictive value in patients with isolated headache suspected of CVT in our meta-analysis that combined data from our own and three previous series. This is comparable with the values found in PE and DVT when a low risk Wells score, based on physical examination, is combined with negative D-dimer. Our meta-analysis describes the largest group of patients with isolated headache studied for the diagnostic value of D-dimer in recent literature. This is also the only study focusing on low risk CVT patients, making the results valuable for everyday practice.

Our study has limitations. First, insufficient data on isolated headache and concomitant D-dimer levels were available from six potential useful articles [13, 17, 19, 21-23]. We attempted to obtain additional information from the concerned authors but received information from only one [17]. However, we did collect data on a large number of patients allowing a sufficiently precise estimation of the diagnostic value of D-dimer in this low risk group. Second, we could not determine how many headache patients presented to our hospital in whom D-dimer was not determined in this period. Unfortunately, it is not possible to reliably retrieve this information from the hospital information system. This means that in our evaluation very low risk patients may have been missed compromising the generalizability of the findings. On the other hand, the addition of patients from studies performed in other large hospitals in several countries improved the generalizability of our results..

Finally, the D-dimer determination method varied over the cited articles; however, most articles used quantitative latex assays, with high sensitivity with the same cut-off value. It was not possible to calculate D-dimer cut-off levels in this group as exact values were not given in most articles, in particular not in patients without CVT.

We defined patients to have a low risk of CVT when they had a normal neurological examination and normal standard head CT. The definition of a normal neurological examination might be a point of discussion as papillary edema for instance may be difficult to determine reliably and in many cases is not judged by the treating physician at all. In an earlier study patients with papillary edema were included in a cohort with isolated headache [6]. In our group two patients with papillary edema alone had a negative D-dimer, and were excluded from our group of patients with isolated headache. Also a symptom like tinnitus which may be present in raised intra cranial pressure is often not mentioned and could not be included in our definition.

A raised risk of CVT exists during pregnancy and puerperium and in patients using oral contraceptives, but also in older patients and patients with underlying malignancy. These patients are also at risk of having a false positive D-dimer. In the entire group three patients were reported to be pregnant and 22 were reported to be using contraceptives. However, the use of contraceptives or presence of pregnancy in the patients from literature could only be clearly deduced in those with established CVT. The limited number of patients and insufficient reporting of pregnancy and use of contraceptives makes it difficult to give recommendations. Caution in this high risk group seems warranted and we feel these patients should undergo follow up neuro-imaging when CVT is suspected regardless of D-dimer outcome. Of all consecutive patients with CVT there were 1.6% false negative D-dimers. Earlier concerns regarding usability of D-dimer in this patient group was based on percentages found in studies citing percentages of false negative D-dimers ranging from 10-50% [12, 15, 19, 20-22]. However these articles did not mention D-dimer results in non-CVT patients or gave insufficient data on this control group. In our own patient group no false negative D-dimers were found, which was confirmed by three studies, including two large prospective studies [11,17,18]. Including these articles in our meta-analysis, the sensitivity of D-dimer in isolated headache patients for detection of CVT is 87% (95% CI: 79.0%-93.0%). This sensitivity is lower, but comparable to, sensitivity found in various tests used for D-dimer determination in PE and DVT patients [10]. Unfortunately as no matched isolated headache controls are described, the calculation of specificity and the negative and positive predictive value for this entire group is impossible. As the patients in most of these articles were collected over time in tertiary headache referral centers, they may cause an overestimation of CVT, with large numbers of controls balancing them out.

When evaluating the risk for false negative D-dimer this is higher in patients with a single affected sinus and patients with a longer duration of complaints [14]. Unfortunately information on both these parameters was only available in a small number of patients and conclusions on these factors cannot be drawn from our data. These parameters are an important focus of future prospective research.

In patients with isolated headache D-dimer could become a useful screening tool to exclude CVT and may help reduce unnecessary additional imaging using intra-venous contrast or MRI. In the presence of risk factors for CVT such as pregnancy, puerperium, use of oral contraceptives,

neurological symptoms and abnormalities on standard head CT it remains necessary to perform diagnostic follow-up. As is the case in DVT and PE D-dimers cannot be seen a stand-alone test and must be combined with clinical risk factors. The high negative predictive value of 99.8% may aid the physician in decision making, although a positive result does not prove the presence of CVT due to low positive predictive value. Although sensitivity is lower, it is comparable to sensitivity accepted in excluding PE and DVT. In this series the use of negative D-dimer would have avoided additional neuro-imaging for diagnosing CVT in 502 patients, whereas only 89 patients with false positive D-dimer would have been scanned unnecessarily. One patient would have been missed. Prospective studies confirming our findings concerning low risk CVT patients are needed.

REFERENCES

1. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35:664-70
2. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F; ISCVT Investigators. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics. Stroke. 2008;39:1152-8.
3. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal Neurology Neurosurgery Psychiatry 2005;76:1084-1087.
4. de Bruijn SF, Stam J, Kappelle. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet. 1996;348(9042):1623-1625.
5. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. Neurology. 1999 22;53:1537-42.
6. Gameiro J, Ferro JM, Canhão P, Stam J, Barinagarrementeria F, Lindgren A. Prognosis of cerebral vein thrombosis presenting as isolated headache: early vs. late diagnosis.; International Study on Cerebral Vein and Dural Sinus Thrombosis investigators. Cephalalgia. 2012 32:407-12.
7. Scarvelis D, Wells PS. Diagnosis of and treatment of deep vein trombosis. CMAJ. 2006 24;175:1087-92.
8. Agnelli G, Becattini C.Acute pulmonary embolism. N Engl J Med. 2010 15;363:266-74.
9. Stein PD, Woodard PK, Weg JG, Wakefield TW, Tapson VF, Sostman HD, Sos TA, Quinn DA, Leeper KV Jr, Hull RD, Hales CA, Gottschalk A, Goodman LR, Fowler SE, Buckley JD, PIOPED II investigators Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. Am J Med. 2006;119:1048.
10. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;2:296-304.
11. Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2012;10:582-9
12. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:1158-92
13. Crassard I, Soria C, Tzourio C, Woimant F, Drouet L, Ducros A, Bousser MG. A negative D-dimer assay does not rule out cerebral venous thrombosis: a series of seventy-three patients. Stroke 2005;36:1716–19
14. Kosinski CM, Mull M, Schwarz M, Koch B, Biniek R, Schlafer J, Milkereit E, Willmes K, Schiefer J. Do normal D-dimer levels reliably exclude cerebral sinus thrombosis? Stroke 2004; 35: 2820–5
15. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 18;155:529-36.

16. Tardy B, Tardy-Poncet B, Viallon A, Piot M, Garnier P, Mohamedi R, Guyomarc'h S, Venet C. D-dimer levels in patients with suspected acute cerebral venous thrombosis. Am J Med. 2002 15;113:238-41

17. Meng R, Wang X, Hussain M, Dornbos D 3rd, Meng L, Liu Y, Wu Y, Ning M, Ferdinando S B, Lo EH, Ding Y, Ji X. Evaluation of plasma D-dimer plus fibrinogen in predicting acute CVST. Int J Stroke. 2014 9:166-73.

18. Tanislav C, Siekmann R, Sieweke N, Allendörfer J, Pabst W, Kaps M, Stolz E. Cerebral vein thrombosis: clinical manifestation and diagnosis. BMC Neurol. 2011 10;11:69.

19. Lalive PH, de Moerloose P, Lovblad K, Sarasin FP, Mermillod B, Sztajzel R. Is measurement of D-dimer useful in the diagnosis of cerebral venous thrombosis? Neurology, 2003;61:1057-60.

20. Gouda T, Sabry M. Evaluation of Plasma D-Dimer Assay as A Diagnostic Biomarker for Cerebral Venous Thrombosis. Egypt J Neurol Psychiat Neurosurg. 2010; 47: 331-336)

21. Cucchiara B, Messe S, Taylor R, Clarke J, Pollak E. Utility of D-dimer in the diagnosis of cerebral venous sinus thrombosis. J Thromb Haemost. 2005;3:387-9.

22. Misra UK, Kalita J, Bansal V. D-dimer is useful in the diagnosis of cortical venous sinus thrombosis. Neurol India. 2009;57:50-4.

23. Hiltunen S, Putaala J, Haapaniemi E, Salonen O, Tatlisumak T. D-dimer and clinicoradiologic features in cerebral venous thrombosis. J Neurol Sci. 2013;15;327:12-4.

24. M Ghaffarpour, N Mohsenzadeh, H Poormahmoodian, M Harrirchian, A Fallah. Diagnostic value of D-dimer measurement in patients suspected of having cerebral venous thrombosis. Acta Medica Iranica 2008. 46:481-484.

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.

REFERENCES

1. LP Savitz Levitan EB, Wears R, Edlow JA. Pooled analysis of patients with thunderclap headache evaluated by CT Journal of Neurological Science 2009 15 276:123-125.
2. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. Journal Neurology Neurosurgery Psychiatry 2005 76:1084-1087.
3. Maruyama H, Nagoya H, Kato Y, et al. Spontaneous cervicocephalic arterial dissection with headache and neck pain as the only symptom. Journal Headache Pain. 2012 13:247-253.
4. Mitsias P, Ramadan NM Headache in ischemic cerebrovascular disease. Part I: Clinical features. Cephalalgia. 1992 12:269-274.
5. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm Lancet. 1986 29 2:1247-1248
6. Ducros A, Reversible vasoconstriction syndrome. Lancet Neurol 2012; 11: 906–17
7. Han A, Yoon DY, Kim ES, Kim HC, Cho BM, Lee JY. Value of CT angiography for the detection of intracranial vascular lesions in patients with acute severe headache. Eur Radiol. 2013 23:1443-9.
8. Greving JP, Wermer MJ, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. Lancet Neurol.2014 1:59-66.
9. Day JW, Raskin NH. Thunderclap headache symptom of unruptured aneurysm Lancet. 1986 29;2:1247-1248
10. Raps EC, Rogers JD, Galetta SL et al. The clinical spectrum of unruptured intracranial aneurysms. 1993; Arch neurology;50:265-268 .
11. Witham TF, Kaufmann AM. Unruptured cerebral aneurysm proceeding a thunderclap headache. Emergency Medicine. 2000 18:88-90
12. McCarron MO, Choudhari KA. Aneurysmal subarachnoid leak with normal CT and CSF spectrophotometry Neurology 2005 8;64:923.
13. Yield of CT angiography in patients with acute headache, normal neurological examination and normal non-contrast CT: a meta-analysis. I.M.E. Alons MD, B.F.J. Goudsmit, K. Jellema MD PhD, M.A.A. van Walderveen MD PhD, Wermer MJH MD PhD, A. Algra MD Ph[4]
14. Development of a clinical prediction model for optimizing the diagnostic yield of CT angiography in patients with acute headache; to scan or not to scan? I.M.E. Alons MD, B.F.J. Goudsmit, K. Jellema MD PhD, M.A.A. van Walderveen MD PhD, Wermer MJH MD PhD, A. Algra MD Ph[4]
15. Arora S, Swadron SP, Dissanayake V. Evaluating the sensitivity of visual xanthochromia in patients with subarachnoid hemorrhage. J Emerg Med. 2010 39:13-6.
16. Jereb M, Muzlovic I, Hojker S, Strle F: Predictive value of serum and cerebrospinal fluid procalcitonin levels for the diagnosis of bacterial meningitis. Infection. 29:209-12, 2001
17. Konstantinidis T, Cassimos D, Gioka T, Tsigalou C, Parasidis T, Alexandropoulou I, et al: Can procalcitonin in cerebrospinal fluid be a diagnostic tool for meningitis? J Clin Lab Anal. 2014 29:169-74

18. Crassard I, Soria C, Tzourio C, Woimant F, Drouet L, Ducros A, Bousser MG. A negative D-dimer assay does not rule out cerebral venous thrombosis: a series of seventy-three patients. Stroke 2005 36:1716–19

19. Kosinski CM, Mull M, Schwarz M, Koch B, Biniek R, Schlafer J, Milkereit E, Willmes K, Schiefer J. Do normal D-dimer levels reliably exclude cerebral sinus thrombosis? Stroke 2004 35: 2820–5

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.

NEDERLANDSE SAMENVATTING

Hoofdpijn is een veel voorkomende klacht waarmee patiënten zich op de spoedeisende hulp presenteren. De taak van de neuroloog bestaat eruit de onschuldige, maar vaak zeer belastende, primaire hoofdpijnen (bijv. migraine, clusterhoofdpijn en tension type hoofdpijn) te onderscheiden van de mogelijke fatale secundaire hoofdpijnen zoals subarachnoïdale bloeding (SAB), cerebraal veneuze trombose (CVT), reversibel cerebraal vasoconstrictie syndroom, dissectie of meningitis.

Dit proefschrift richt zich op verschillende diagnostische onderzoeken om de oorzaken van deze typen hoofdpijn vast te stellen. Het doel is niet alleen het evalueren van de onderzoeken zelf, maar ook wanneer en bij welke patiënten het onderzoek in te zetten.

Een groot deel van dit proefschrift is gewijd aan het beoordelen van de opbrengst van de CT angiografie bij verschillende groepen patiënten met hoofdpijn op de spoedeisende hulp. Bij patiënten met acute hoofdpijn en een normaal neurologisch onderzoek en normale blanco CT scan van de hersenen lijkt er een licht verhoogd aantal afwijkingen te worden gevonden. In ons eerste onderzoek naar dit onderwerp vonden wij bij 13 (19%) van 70 patiënten een afwijking (hoofdstuk 2). Een aanzienlijk deel van deze patiënten had een neuro-vasculaire episode doorgemaakt zoals een eerdere SAB of CVT. Verder waren deze patiënten geïncludeerd op basis van een verrichte ruggenprik met normale uitkomst. Dit was in de periode voordat onderzoek uitwees dat indien binnen 6 uur van het ontstaan van de hoofdpijn er een blanco CT is verricht, er geen ruggenprik meer hoeft te gebeuren. Hierdoor is mogelijk al een strengere selectie van patiënten opgetreden, omdat een ruggenprik een belastend onderzoek is.

Ons volgende onderzoek was gebaseerd op een recentere populatie uit zowel het Leids Universitair Medisch Centrum als het Haaglanden Medisch Centrum en verder op patiënten uit de literatuur. In de meta-analyse, vonden wij een afwijking bij 7% van de patiënten (hoofdstuk 3). De meeste afwijkingen betroffen aneurysmata waarvan de klinische betekenis niet geheel duidelijk is. Ongeveer 2-3% van de bevolking heeft een intracranieel aneurysma; wij vonden een aneurysma bij 5.4% van de patiënten. Het was in de onderzoeksgroep niet goed te achterhalen bij hoeveel van de gevonden aneurysmata er een bloeding optrad, aangezien niet in alle gevallen bekend was of er bilirubine in het hersenvocht werd bepaald. Dit is relevant om te achterhalen of het een niet gebarsten aneurysma, dat is een toevalsbevinding, betreft. In een klein aantal gevallen werd een zekere klinisch relevante bevinding gedaan. Wij stelden een trombose van de venen van de hersenen vast bij drie patiënten (0.5%), een reversibel vasoconstrictie syndroom bij vier patiënten (0.5%), een Moya-Moya bij twee patiënten (0.3%), een arteriële dissectie bij twee (0.3%) en een herseninfarct bij één patiënt (0.1%). Het aantal patiënten dat gescand moest worden om enigerlei afwijking te vinden was 14 en het aantal om een klinisch relevante afwijking te vinden was 61. Het lijkt erop dat het aantal gevonden klinisch relevante afwijkingen bij patiënten met acute hoofdpijn en normale bevindingen bij neurologisch onderzoek en blanco CT klein is. Dit

komt overeen met het eerder vastgestelde gunstige beloop bij deze groep bij follow-up studies. De afwijkingen welke wél worden gevonden zijn echter bedreigend en vereisten het geven van medicatie of intensievere follow-up. Daarom is het definitief ontraden van een CTA bij deze groep een brug te ver. Een prospectieve studie om de diagnostische opbrengst te beoordelen loopt momenteel in het Leids Universitair Medisch Centrum en Haaglanden Medisch Centrum.

Naast de patiënten met een normaal neurologisch onderzoek en normale blanco CT scan hebben we ook gekeken naar factoren die het vinden van afwijkingen op CTA beïnvloeden bij patiënten met acute hoofdpijn in het algemeen die zich op de spoedeisende hulp presenteren (hoofdstuk 4). Het blijkt dat verschillende factoren hierbij mee spelen, maar een afwijkende blanco CT alleen is al zo'n sterke voorspeller dat het toevoegen van andere voorspellende factoren de waarde van de blanco CT niet overtreft. Hoewel dit nogal een open deur lijkt, is het goed om te weten dat de kans om een afwijking te vinden bij een normale blanco CT zeer klein is. We vonden nog wel een klein aantal afwijkingen dat wel verdere behandeling behoefde.

Bij sommige patiënten is het toch nodig om het hersenvocht te onderzoeken op tekenen van een doorgemaakte bloeding. Dit kan door het bepalen van de aanwezigheid van bloedafbraakproducten, zoals bilirubine met fotospectometrie. Hierbij wordt de bekende resonantiegolflengte van de bloedafbraakproducten gebruikt om de aanwezigheid ervan in het hersenvocht te bepalen. Wij vergeleken twee methoden om deze bepaling te beoordelen (hoofdstuk 5). De Leiden methode is een rekenmethode gebruikt in combinatie met fotospectometrie en deze heeft een sensitiviteit van 100%. De specificiteit wordt echter verlaagd als er veel eiwit in het hersenvocht aanwezig is of als een patient veel bilirubine in het bloed heeft. De specificiteit kan verbeterd worden door het toepassen van de UK NEQAS methode indien de Leiden methode afwijkingen toont. Bij de UK NEQAS wordt een aanvullende beoordeling door de klinisch chemicus verricht met een beslisboom. Door de twee methoden in deze volgorde te gebruiken kan een maximale sensitiviteit en specificiteit worden bereikt zonder dat er een overmatige werkbelasting ontstaat.

In bepaalde gevallen zou het ook mogelijk kunnen zijn om aanvullende beeldvorming te voorkomen. Bij patiënten met een verdenking op trombose van de afvoerende hersenvaten of venen, wordt frequent aanvullend CT venografie of MRI verricht om dit uit te sluiten danwel aan te tonen. D-dimeer is een stollingseiwit dat wordt bepaald bij de diagnostiek rondom longembolieën en diep veneuze trombose. Bij patiënten met een op klinisch bepaalde gronden laag risico op diep veneuze trombose en longembolieën en een normaal D-dimeer is uit eerder onderzoek gebleken dat het niet nodig is aanvullende beeldvorming te verrichten. In dit proefschrift is onderzocht of bij patiënten met een laag risico op cerebrale veneuze trombose beeldvorming vermeden kan worden bij een normaal D-dimeer (hoofdstuk 7). In een groep van 636 patiënten hadden er 45 een cerebrale veneuze trombose. Daarvan had er één een fout negatieve D-dimeer (7.5 %). De sensitiviteit van D-dimeer voor het stellen van de diagnose cerebrale veneuze trombose was 97.8 % (95 % betrouwbaarheidsinterval(BI): 88.2-99.6 %), de specificiteit 84.9 % (95 % BI: 81.8-87.7 %), de positief voorspellende waarde 33.1 % (95 % BI: 25.2-

41.7 %) en de negatief voorspellende waarde 99.8 % (95 % BI: 98.9-100%). Het bepalen van een D-dimeer kan worden gebruikt om aanvullende beeldvorming te vermijden bij patiënten met een laag risico op cerebraal veneuze trombose .

Als laatste hebben wij gekeken naar de productie van procalcitonine in het hersenvocht, bij patiënten met de verdenking op een bacteriële meningitis. Procalcitonine is een acute fase eiwit dat wordt aangemaakt bij bacteriële ontstekingen. In serum is aangetoond dat hiermee onderscheid gemaakt kan worden tussen septische of aseptische ontstekingsreacties. In hersenvocht wordt procalcitonine waarschijnlijk aangemaakt door gliacellen. In ons prospectieve onderzoek toonden wij aan dat procalcitonine significant verhoogd is bij patiënten met een bacteriële meningitis ten opzichte van patiënten met acute hoofdpijn of een virale meningitis (hoofdstuk 6). Verder is bij patiënten met een bacteriële meningitis na een neurochirurgische interventie de procalcitonine spiegel relatief veel sterker verhoogd in de liquor dan in het serum. Deze scheve verdeling lijkt erop te duiden dat procalcitonine in de hersenen of hersenvliezen zelf word aangemaakt in plaats van bijvoorbeeld door bloedbijmenging rondom de liquorpunctie. Al met al lijkt procalcitonine een veelbelovende marker te zijn rondom de diagnostiek van bacteriële meningitis.

Naar aanleiding van de hier besproken onderzoeken zij nu meerdere studies gaande. Een prospectief multicenter onderzoek is bezig waarbij de opbrengst van CT angiografie bij patiënten met acute hoofdpijn, een normaal neurologisch onderzoek en een normale blanco CT wordt bekeken. Ook zal worden gekeken naar het opnieuw optreden van episoden met acute hoofdpijn in onze retrospectieve patiënten groep. Als laatste loopt op dit moment een onderzoek naar de hoogte van het procalcitonine van dag tot dag bij patiënten met een externe ventrikel drain na een doorgemaakte bloeding.

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CURRICULUM VITAE

Imanda Maria Elisabeth (Manda) werd op 21 januari 1983 geboren in Amsterdam. In 2001 behaalde zij haar VWO diploma aan het Vossius Gymnasium te Amsterdam en dat jaar begon zij haar geneeskunde studie aan de Rijksuniversiteit in Groningen. In 2004 deed zij een internationale stage neurologie in Finland, waar haar interesse in het vak werd gewekt. Zij volgde twee semi-arts stages neurologie; in het Academisch Medisch Centrum in Amsterdam en tevens in het Haaglanden MC te den Haag.

Na het behalen van haar Geneeskunde diploma in 2009 werkte zij als ANIOS neurologie in het Kennemergasthuis in Haarlem. In mei 2010 begon zij haar opleiding tot neuroloog in het Haaglanden MC Met als opleider dr. Vecht en later prof. Taphoorn.

Door gezinsuitbreiding en werk van haar man in Groningen heeft Manda de laatste 2 jaar van haar opleiding in het Universitair Medisch Centrum Groningen afgerond. In deze periode deed zij een differentiatie stage bewegingsstoornissen onder begeleiding van prof. M.A.J. de Koning-Tijssen en prof. T. van Laar. Het zwaartepunt van de stage lag bij de ziekte van Parkinson. Aanvullend deed zij een tweede differentiatie stage bij de geriatrie onder begeleiding van dr. D.Z.B. van Asselt. Aandachtsgebied tijdens deze stage was cognitieve stoornissen en zorg voor de oudere patient met multiproblematiek.

Gedurende haar opleiding heeft Manda naast het onderzoek voor het voltooien van haar proefschrift deelgenomen aan de studie “Corticosteroid injection in patients with ulnar neuropathy at the elbow: A. randomized, double-blind, placebo-controlled trial” en gepubliceerd in Muscle Nerve in 2014.

Sinds juli 2016 is Manda werkzaam als neuroloog in het Meander MC te Amerfoort met als aandachtsgebied de ziekte van Parkinson en cognitieve stoornissen. Zij woont samen met Robert Nijborg in Soest en heeft drie dochters; Benthe, Elke en Linde.

LIJST VAN PUBLICATIES

- Yield of CT angiography in patients with acute headache, normal neurological examination and normal. non-contrast CT: a meta-analysis. Accepted for publication in Journal of Stroke and Cerebrovascular disease, dec 2017.

- Procalcitonin in cerebrospinal fluid in meningitis; a prospective diagnostic study. Brain Behav. 2016 16;6(11).

- D-dimer for the exclusion of cerebral venous thrombosis: a meta-analysis of low risk patients with isolated headache. Imanda M.E. Alons, Korné Jellema, Marieke J.H. Wermer and Ale Algra. BMC Neurology (2015) 15:118

- The value of CT angiography in patients with acute severe headache. I.M.E. Alons MD, I.R. van den Wijngaard MD, R.J. Verheul PhD, G. Lycklama à Nijeholt MD PhD, M.J.H. Wermer MD PhD, A. Algra MD PhD, K. Jellema MD PhD. Acta Neurol Scand. 2014 Oct 14.

- Corticosteroid injection in patients with ulnar neuropathy at the elbow: A. randomized, double-blind, placebo-controlled trial. van Veen KE(1), Alblas KC, Alons IM, Kerklaan JP, Siegersma MC, Wesstein M, Visser LH, van Kasteel V, Jellema K. Muscle Nerve, 2014 Dec 19.

- Optimizing blood pigment analysis in cerebrospinal fluid for the diagnosis of subarachnoid haemorrage – A practical approach. I.M.E Alons, R. Verheul, G.A.E. Ponjee, K. Jellema. Eur J Neurol. 2013 Jan; 20(1):193-7.

- Prediction of abnormalities at CT angiography in patients with acute headache. Imanda M.E. Alons MD, Ben F.J. Goudsmit, Korné Jellema MD PhD, Marianne A.A. van Walderveen MD PhD, Marieke J.H. Wermer MD PhD, Ale Algra MD PhD. Accepted for publication in Brain and Behavior, april 2018.