CT within 6 hours of headache onset to rule out subarachnoid hemorrhage in nonacademic hospitals

Katelijn M. Blok, MD
Gabriel J.E. Rinkel, MD, FRCP(E)
Charles B.L.M. Majoie, MD, PhD
Jeroen Hendrikse, MD, PhD
Meriam Braaksma, MD
Cees C. Tijssen, MD, PhD
Yu Yi Wong, MD
Jeannette Hofmeijer, MD, PhD
Jorunn Extercatte, MD
Bertjan Kerklaan, MD
Tobien H.C.M.L. Schreuder, MD
Susanne ten Holter, MD
Freek Verheul, MD
Laurike Harlaar, MD
D. Martijn O. Pruissen, MD, PhD
Vincent I.H. Kwa, MD, PhD
Paul J. Brouwers, MD, PhD
Michel J.M. Remmers, MD, MSc
Wouter J. Schonewille, MD, PhD
Nyika D. Kruyt, MD, PhD
Mervyn D.I. Vergouwen, MD, PhD

Correspondence to Dr. Vergouwen: m.d.i.vergouwen@umcutrecht.nl

ABSTRACT

Objective: To investigate whether staff radiologists working in nonacademic hospitals can adequately rule out subarachnoid hemorrhage (SAH) on head CT <6 hours after headache onset.

Methods: In a multicenter, retrospective study, we studied a consecutive series of patients presenting with acute headache to 11 nonacademic hospitals. Inclusion criteria were (1) normal level of consciousness without focal deficits, (2) head CT <6 hours after headache onset and reported negative for the presence of SAH by a staff radiologist, and (3) subsequent CSF spectrophotometry. Two neuroradiologists and one stroke neurologist from 2 academic tertiary care centers independently reviewed admission CTs of patients with CSF results that were considered positive for presence of bilirubin according to local criteria. We investigated the negative predictive value for detection of SAH by staff radiologists in nonacademic hospitals on head CT in patients scanned <6 hours after onset of acute headache.

Results: Of 760 included patients, CSF analysis was considered positive for bilirubin in 52 patients (7%). Independent review of these patients' CTs identified one patient (1/52; 2%) with a perimesencephalic nonaneurysmal SAH. Negative predictive value for detection of subarachnoid blood by staff radiologists working in a nonacademic hospital was 99.9% (95% confidence interval 99.3%–100.0%).

Conclusions: Our results support a change of practice wherein a lumbar puncture can be withheld in patients with a head CT scan performed <6 hours after headache onset and reported negative for the presence of SAH by a staff radiologist in the described nonacademic setting. ***Neurology*®** **2015;84:1–6**

GLOSSARY

CI = confidence interval; **NPV** = negative predictive value; **SAH** = subarachnoid hemorrhage.

Recently, 2 studies showed that in patients presenting with acute headache suspicious of aneurysmal subarachnoid hemorrhage (SAH), the negative predictive value (NPV) of head CT scan performed within 6 hours after headache onset is 100% if the scan is made on a third-generation CT scanner performed in a university-affiliated tertiary care teaching hospital and interpreted by a neuroradiologist or general radiologist who routinely reports head CT images.[1,2] The clinical implication of these studies was that a lumbar puncture is no longer needed to exclude a diagnosis of SAH in the described academic setting. The purpose of this study was to investigate whether this change of practice can be extrapolated to nonacademic hospitals.

METHODS

We studied a multicenter, retrospectively collected consecutive series of patients in 11 nonacademic hospitals in the Netherlands. All participating centers were equipped with third-generation CT scanners. Characteristics of participating hospitals are shown in the table. We included all patients presenting between January 2007 and January 2013 with spontaneous acute

From the Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus (K.M.B., G.J.E.R., M.D.I.V.), and Department of Radiology (J. Hendrikse), University Medical Center Utrecht; Department of Radiology (C.B.L.M.M.), Academic Medical Center, Amsterdam; Department of Neurology (M.B., C.C.T.), St. Elisabeth Hospital, Tilburg; Department of Neurology (Y.Y.W., J. Hofmeijer), Rijnstate Hospital, Arnhem; Department of Neurology (J.E., B.K.), Sint Lucas Andreas Hospital, Amsterdam; Department of Neurology (T.H.C.M.L.S.), Atrium Medical Center, Heerlen; Department of Neurology (S.t.H., F.V.), Groene Hart Hospital, Gouda; Department of Neurology (L.H., D.M.O.P.), Diakonessenhuis, Utrecht; Department of Neurology (V.I.H.K.), Onze Lieve Vrouwe Gasthuis, Amsterdam; Department of Neurology (P.J.B.), Medisch Spectrum Twente, Enschede; Department of Neurology (M.J.M.R.), Amphia Hospital, Breda; Department of Neurology (W.J.S.), St. Antonius Hospital, Nieuwegein; and Department of Neurology (N.D.K.), Slotervaart Hospital, Amsterdam, the Netherlands. N.D.K. is currently affiliated with the Department of Neurology, Leiden University Medical Center, the Netherlands.

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Table Characteristics of participating nonacademic hospitals

Center	No. of ER visits/y	No. of head CT scans/y	No. of beds on neurology ward	No. of SAH diagnoses/y
1	13.397	1.567	10	3
2	21.500	2.700	30	12
3	25.500	3.280	25	12
4	26.325	2.682	41	33
5	27.862	5.171	40	100 (nonacademic tertiary referral hospital)
6	28.000	3.051	30	8
7	31.974	5.387	45	28
8	33.614	3.631	29	8
9	39.007	4.602	34	20
10	38.743	5.291	40	21
11	46.219	3.391	24	15

Abbreviations: ER = emergency room; SAH = subarachnoid hemorrhage.

headache suspected of SAH, who had a head CT scan within 6 hours after headache onset that was reported negative for the presence of subarachnoid blood by a staff radiologist, and subsequent CSF spectrophotometry. We decided beforehand to also include patients with a CT initially being reported negative for the presence of SAH, but subsequently judged positive after positive CSF spectrophotometry became available. Exclusion criteria were as follows: (1) Glasgow Coma Scale score ≤14 at presentation, (2) unknown time of ictus, (3) age 16 years or younger, and (4) lumbar puncture performed earlier than 12 hours after headache onset. CSF was analyzed by spectrophotometry and interpreted according to local criteria. In the participating centers, spectrophotometric results were analyzed with the following methods: oxyhemoglobin/bilirubin concentration (n = 3),[3] UK NEQAS (National External Quality Assessment Service) method (n = 2),[4] qualitative assessment of absorption curve (n = 2),[5] Leiden method (n = 2),[6] and bilirubin excess (n = 2).[7]

As the gold standard for interpretation of the admission CTs, 2 experienced neuroradiologists and one experienced stroke neurologist from 2 academic tertiary care hospitals (one reading by C.B.L.M.M. in AMC; other reading jointly by J. Hendrikse and G.J.E.R. in UMCU) independently reviewed all admission CT scans of patients with a positive finding of bilirubin according to the local CSF analysis protocol. The reviewers of the head CTs were blinded for any clinical or radiologic follow-up information. For purposes of analysis, disagreements between reviewers were resolved via a consensus meeting. We calculated the NPV (95% confidence interval [CI]) for detection of subarachnoid blood on admission head CT by staff radiologists working in a nonacademic hospital.

For patients with CSF results that were initially interpreted as positive for SAH by local criteria and a negative head CT on independent review, the results of additional cerebrovascular imaging were obtained, and the patients' hospital records were reviewed for readmissions for SAH. For patients in whom an aneurysm was found on vascular imaging, the aneurysm was considered an incidental, unruptured aneurysm if the initial CSF results were considered falsely positive based on one of the following criteria: (1) the sample contained $<100 \times 10^6$/L red blood cells in CSF,[8] (2) an alternative explanation for the positive CSF result was found, or (3) a second method of CSF spectrophotometric analysis showed negative results; for example, bilirubin-excess value 0.24 (>0.20 is abnormal), but absorption units at 450 to 460 nm <0.05.

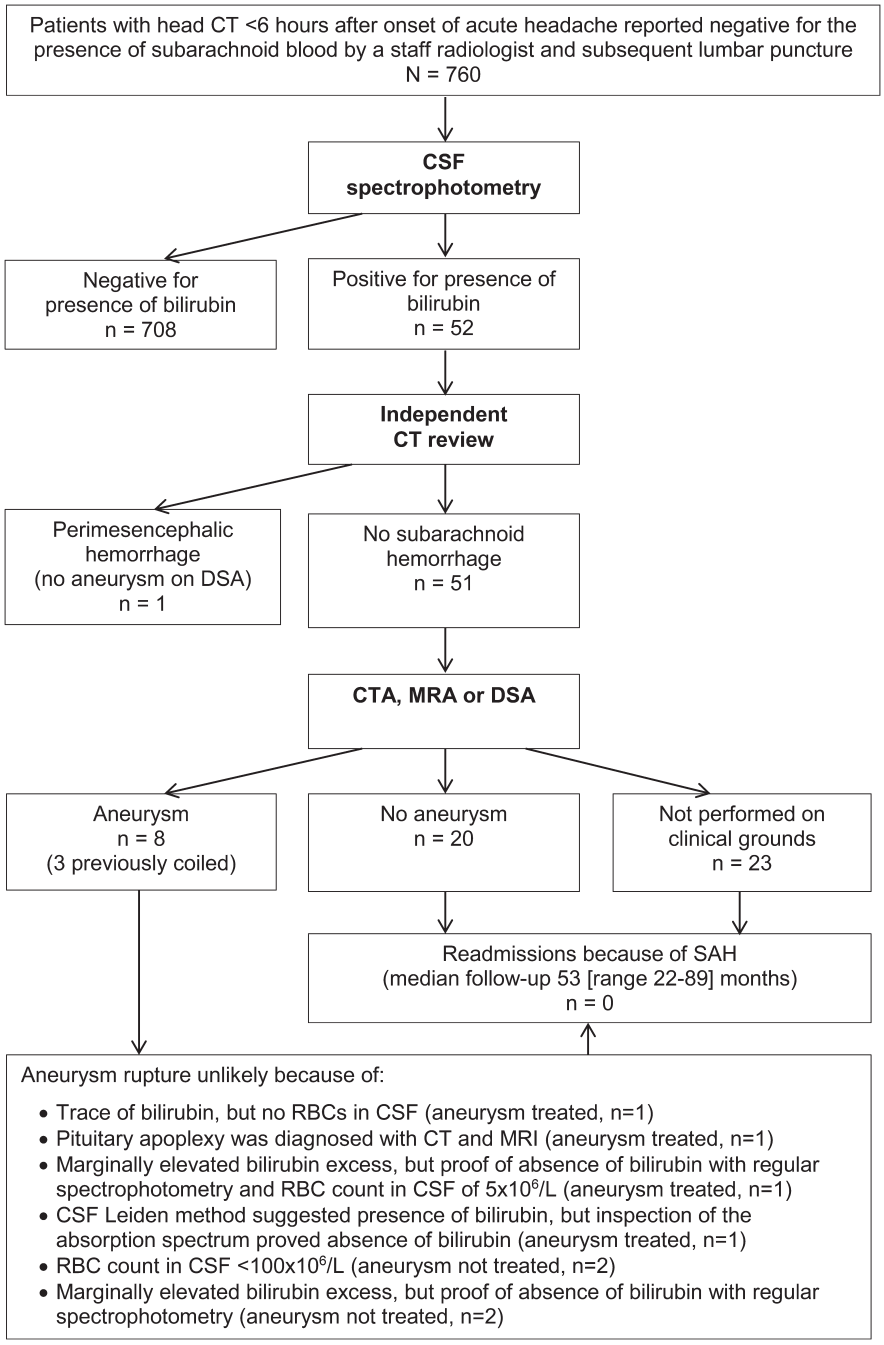
Standard protocol approvals, registrations, and patient consents. A nationwide approval of the study was given by the institutional research ethics board of the University Medical Center Utrecht.

RESULTS During the study period, 760 patients underwent head CT within 6 hours after onset of acute headache, followed by lumbar puncture >12 hours after headache onset (figure 1). The median age was 45 years (range 17–87) and 466 patients (61%) were female. In total, the CSF results of 52 patients (7%) were initially considered positive for SAH by local spectrophotometric criteria. In both independent readings of the admission head CTs of these 52 patients, the reviewers reported subarachnoid blood in one (the same) patient. In both readings, the bleeding pattern was considered to be perimesencephalic. Since digital subtraction angiography did not reveal an aneurysm in this patient, the diagnosis nonaneurysmal perimesencephalic hemorrhage was made on review (figure 2). This patient had a benign clinical course with no readmission for SAH in 26 months of clinical follow-up. No subarachnoid blood was identified in the other 51 patients. The NPV for detection of subarachnoid blood by staff radiologists working in a nonacademic hospital was 99.9% (95% CI 99.3%–100.0%). It was unlikely that any of the 51 patients without subarachnoid blood on head CT and positive or false-positive CSF spectrophotometric results had a missed diagnosis of SAH (figure 1).

DISCUSSION The results of this multicenter study show that the NPV for detection of subarachnoid blood on a CT scan made within 6 hours after headache onset by staff radiologists working in nonacademic hospitals was 99.9%. Of 760 patients presenting with acute headache, one patient with subarachnoid blood in the basal cisterns was missed. This patient had a perimesencephalic pattern of subarachnoid blood on initial CT reading, a negative digital subtraction angiogram, and a benign clinical course with no readmission for SAH on follow-up. Therefore, this case is consistent with nonaneurysmal perimesencephalic SAH.

Two other large studies investigated test characteristics of CT scans <6 hours after symptom onset: a Canadian prospective study in 11 emergency departments of university-affiliated teaching hospitals,[1] and a Dutch retrospective study in a Dutch tertiary care university hospital.[2] Both studies included consecutive patients and used third-generation CT scanners. The NPV for SAH in patients with acute onset of headache was 100.0% (95% CI 99.5%–100.0%) in the Canadian study and 100.0% (95% CI 94.8%–100.0%) in the Dutch study.

Figure 1 Flowchart



Flowchart of included patients. CTA = CT angiography; DSA = digital subtraction angiography; MRA = magnetic resonance angiography; RBC = red blood cell; SAH = subarachnoid hemorrhage.

A third study on the predictive value of CT scanning in patients with acute headache was a retrospective study describing 11 patients from 21 emergency departments between 2000 and 2011 with acute headache, a head CT <6 hours after onset of acute headache, and a subsequent positive lumbar puncture.[9] This study was criticized for 2 main reasons.[10,11] First, the 11 false-negative head CTs were not independently reevaluated. Second, diagnosis of aneurysmal SAH was based on the presence of red blood cells in CSF but without xanthochromia, and findings of an arteriovenous malformation or aneurysm on plain CT. Apart from this small and critically reviewed case series, we found no other studies than ours focusing on the predictive value of CT scanning in nonacademic hospitals.

Despite the high NPV in our study, we found that reading of CT scans within 6 hours after onset of headache to rule out the presence of subarachnoid blood is not perfect in large nonacademic hospitals. Therefore, several points should be considered before

Figure 2 Initially misinterpreted head CT scan of a patient with perimesencephalic hemorrhage

deciding to withhold a lumbar puncture in the described setting. First, although no cases of aneurysmal SAH were missed, a perimesencephalic bleeding pattern, which was undiagnosed in one of the patients in our study, is caused by a ruptured aneurysm in 1 of 20 patients.[12] Thus, if lumbar puncture should no longer be performed, an aneurysmal SAH will be missed in 1 of approximately 15,200 (760 × 20) patients with acute headache and a negatively read CT scan. It can be questioned, however, whether 15,200 patients should undergo a lumbar puncture to prevent an aneurysmal SAH in one of them. A lumbar puncture is associated with discomfort for the patient, costs, and may induce a potentially life-threatening complication such as subdural hematoma or cerebral venous sinus thrombosis in rare cases.[13] Second, in this era of sensitive third-generation CT scanners, only selected patients undergo a lumbar puncture, resulting in many false-positive results, as was observed in our study. This will lead to additional CT, magnetic resonance, or digital subtraction angiographies, which may cause further confusion because incidental, asymptomatic aneurysms will be found in approximately 3% of these patients.[14] In our study, 8 patients with false-positive CSF results had an aneurysm on subsequent vascular imaging, which in retrospect were considered to be incidental and unruptured. These cases illustrate the potential harm of performing unnecessary lumbar punctures to diagnose SAH in patients with negative head CT. If an aneurysm is found, the patient and physician are confronted with the difficult decision of either a potentially morbid operation or anxiety-provoking observation. In addition, cerebral digital subtraction angiography is associated with a 1% risk of stroke and other complications.[15] In the setting we studied, CSF spectrophotometry has a positive predictive value of <5%.[16] Using a Bayesian approach, a lumbar puncture is not a useful test to diagnose SAH in the described setting since in our study the pretest probability of having SAH was 0.1%, which increased to a posttest probability of 1.9% in case of a positive CSF spectrophotometric result. Third, the health care system in the Netherlands may differ from that in other countries. The Netherlands has a population of 16.8 million people and 87 hospitals, including 8 academic centers, with access to emergency medical care for all inhabitants. The majority of centers participating in our study were large nonacademic hospitals. Although we assume that our results can easily be extrapolated to countries with similar residency programs for radiologists (5-year training in the Netherlands) and comparable health care systems, this will be more difficult in countries with shorter residency programs and many rural hospitals with low numbers of patients. Fourth, head CT scans could not reliably be assessed to exclude the presence of subarachnoid blood if previously treated aneurysms caused scattering artifacts. In these instances, a lumbar puncture would still be needed to fully rule out the presence of subarachnoid blood. Fifth, during out-of-office hours, CT scans are frequently read by radiology and neurology residents. Because of the design of our study, we could only include patients whose head CT was reported negative by a staff radiologist. We could not retrieve whether and how often CT scans were initially read false-negative by residents. In a previous study, several scans were misinterpreted during out-of-office hours by radiology residents and emergency room physicians.[1] Therefore, we recommend withholding a lumbar puncture and discharge the patient only after the head CT scan is interpreted by a staff radiologist.

A strength of our study is the large number of patients included from 11 nonacademic hospitals, which had varying levels of exposure to patients with SAH ranging from less than 10 to approximately 100 SAH discharge diagnoses per year. We also purposely included a large nonacademic center, because from previous studies, it remained unclear whether a lumbar puncture could be withheld after a negative head CT in large nonacademic centers. The large number of patients and range of hospital sizes increase the generalizability of our findings. In addition, a lumbar puncture was performed in all 760 patients. We used spectrophotometry, which has superior diagnostic accuracy compared with visual inspection of xanthochromia.[17] Therefore, our results also apply to other countries where visual inspection of xanthochromia is more common than spectrophotometry. A limitation of our study was the retrospective design. However, it

is probably unfeasible to prospectively investigate this in nonacademic hospitals. Second, the proportion of patients with no SAH but an aneurysm was higher than expected on the basis of the prevalence of aneurysms in the general population (5/49 = 10.2%; 95% CI 3.4%–22.2%, excluding those with a previously coiled aneurysm). Although the 95% confidence is quite large and compatible with the prevalence in the general population, we cannot exclude the possibility that in some patients the acute headache with no SAH was still associated with the aneurysm. In 7 patients with a negative head CT and an intracranial aneurysm, we considered the initial CSF results false-positive findings (based on additional CSF analyses). However, since no internationally accepted gold standard for interpretation of CSF spectrophotometry exists, uncertainty remains. Third, our follow-up may have been incomplete since patients may have had SAH and presented to another hospital. Finally, although the NPV was very high, it remains unclear how much of the high NPV resulted from a low pretest probability of SAH and how much from the diagnostic accuracy of the local radiologist.

Because a prospective study in nonacademic hospitals with a large enough number of patients is unlikely to be performed for the current research question, our results are the best achievable evidence to support a change of practice wherein a lumbar puncture can be withheld in patients with a head CT scan performed within 6 hours after headache onset and reported negative for the presence of SAH by a staff radiologist in the described nonacademic setting. However, since we encountered one patient with a perimesencephalic hemorrhage, which was missed on the initial CT scan reading, and perimesencephalic hemorrhage can sometimes be caused by a ruptured aneurysm, aneurysmal SAH could be missed when a lumbar puncture is withheld, although this would be an exceedingly rare but potential occurrence.

AUTHOR CONTRIBUTIONS

M.D.I.V. and G.J.E.R. conceived and designed the study. K.M.B. and M.D.I.V. performed data analysis. All authors participated in the data collection, drafted the manuscript and/or contributed to its revision, and approved the final version.

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REFERENCES

1. Perry JJ, Stiell IG, Sivilotti ML, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: 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. Stroes JW, van Rijn HJ. Quantitative measurement of blood pigments in cerebrospinal fluid by derivative spectrophotometry. Ann Clin Biochem 1987;24:189–197.
4. Cruickshank A, Auld P, Beetham R, et al; UK NEQAS Specialist Advisory Group for External Quality Assurance of CSF Proteins and Biochemistry. Revised national guidelines for analysis of cerebrospinal fluid for bilirubin in suspected subarachnoid haemorrhage. Ann Clin Biochem 2008;45:238–244.
5. Vermeulen M, Hasan D, Blijenberg BG, Hijdra A, van Gijn J. Xanthochromia after subarachnoid haemorrhage needs no revisitation. J Neurol Neurosurg Psychiatry 1989;52:826–828.
6. Duiser HJ, Roelandse FW, Lentjes EG, van Loon J, Souverijn JH, Sturk A. Iterative model for the calculation of oxyhemoglobin, methemoglobin, and bilirubin in absorbance spectra of cerebrospinal fluid. Clin Chem 2001;47:338–341.
7. Apperloo JJ, van der Graaf F, Dellemijn PL, Vader HL. An improved laboratory protocol to assess subarachnoid haemorrhage in patients with negative cranial CT scan. Clin Chem Lab Med 2006;44:938–948.
8. Czuczman AD, Thomas LE, Boulanger AB, et al. Interpreting red blood cells in lumbar puncture: distinguishing true subarachnoid hemorrhage from traumatic tap. Acad Emerg Med 2013;20:247–256.
9. Mark DG, Hung YY, Offerman SR, et al; Kaiser Permanente CREST Network Investigators. Nontraumatic subarachnoid hemorrhage in the setting of negative cranial computed tomography results: external validation of a clinical and imaging prediction rule. Ann Emerg Med 2013;62:1–10.
10. Vergouwen MD, Rinkel GJ. Clinical suspicion of subarachnoid hemorrhage and negative head computed tomographic scan performed within 6 hours of headache onset: no need for lumbar puncture. Ann Emerg Med 2013;61:503–504.
11. Perry JJ, Sivilotti ML, Stiell IG. Pragmatic interpretation of the study of nontraumatic subarachnoid hemorrhage in the setting of negative cranial computed tomography results: external validation of a clinical and imaging prediction rule. Ann Emerg Med 2013;62:435–436.
12. Rinkel GJ, Wijdicks EF, Vermeulen M, et al. Nonaneurysmal perimesencephalic subarachnoid hemorrhage: CT and MR

patterns that differ from aneurysmal rupture. AJNR Am J Neuroradiol 1991;12:829–834.
13. Wilder-Smith E, Kothbauer-Margreiter I, Lämmle B, Sturzenegger M, Ozdoba C, Hauser SP. Dural puncture and activated protein C resistance: risk factors for cerebral venous sinus thrombosis. J Neurol Neurosurg Psychiatry 1997;63:351–356.
14. 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 Neurol 2011;10:626–636.
15. Heiserman JE, Dean BL, Hodak JA, et al. Neurologic complications of cerebral angiography. AJNR Am J Neuroradiol 1994;15:1401–1407.
16. Wood MJ, Dimeski G, Nowitzke AM. CSF spectrophotometry in the diagnosis and exclusion of spontaneous subarachnoid haemorrhage. J Clin Neurosci 2005;12:142–146.
17. Nagy K, Skagervik I, Tumani H, et al. Cerebrospinal fluid analyses for the diagnosis of subarachnoid haemorrhage and experience from a Swedish study: what method is preferable when diagnosing a subarachnoid haemorrhage? Clin Chem Lab Med 2013;51:2073–2086.