Author’s response to reviews

Title: Focal subarachnoid haemorrhage mimicking transient ischaemic attack - do we really need MRI in acute stage?

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To whom it may concern

Cover letter – Revisions of “1012492767112383 - Focal subarachnoid haemorrhage mimicking transient ischaemic attack - do we really need MRI in acute stage”

Munich, 1st of February 2014

Dear Ladies and Gentlemen,

We thank you very much for your substantial, constructive and helpful comments on our article!

Please find attached our point-by-point response to your concerns.

We hope to have met your expectations and are heading forward to hearing from you.

Yours sincerely,

Lorenz Ertl on behalf of all authors.
1. “The description of the various sections is confusing, and sometimes unfocused. It is not clear if the aim of the study is to compare MRI and CT in patients with TIA mimic with fSAH, because cases from the literature included miscellaneous fSAH clinical presentations.”

We added the following sentence in ‘methods’ under ‘subjects’:

“Patients were identified by a retrospective query on all cranial MRI examination reports (n = 7482) in the radiological database of our institution between 01/2010 and 12/2012. The following search terms were used: “siderosis”, “subarachnoid hemorrhage”, “focal SAH”. The primary search yielded 243 patients. Patients were included if they fulfilled the following criteria: 1.) presence of a focal SAH at the cerebral convexity, defined as a linear hyperintensity on FLAIR-images and linear hypointensity in T2*-images in MRI; 2.) patients had received an unenhanced CT scan of the brain prior to the MRI. Patients were excluded if they had obvious causes of bleeding such as 1.) aneurysmal SAH or SAH from other intracranial vascular malformations (n = 45), 2.) traumatic SAH (n = 45), 3.) primary intracerebral bleeding or haemorrhagic brain tumor with extension to the subarachnoid space (n = 25), 4.) derrailment of blood coagulation (n = 3). Finally, we identified seven patients with non-traumatic fSAH during this three year period who met the inclusion and exclusion criteria (table 1). After identification of the patients, demographic and clinical characteristics and the final diagnosis were retrieved from hospital records (table 1). An experienced stroke neurologist (M.S.-D.) verified all clinical symptoms and diagnoses, including clinical history, electroencephalogram (EEG), electrocardiogram, echocardiography and routine blood tests.”

2. “The study population with focal SAH described in the literature should also include patients with TIA mimic presentation (and this is not what the authors present - for example, in the study from ref 7 (Stroke 2011,42:3055-60) 10 and no 24 patients presented as transient neurological symptoms; and the same may be true in some of others studies included)”

In this work, we focussed on the neuroradiologic diagnosis of fSAH. Therefore, patients were identified by the electronic search of the radiologic database, but not by the initially suspected clinical diagnosis. In our series, clinical presentation ranged from patients with transient neurological attacks with focal symptoms, which are attributable to dysfunction of one arterial territory of the brain, to patients with diffuse, nonlocalizing cerebral symptoms (e.g., confusion and disorientation). This is in accordance with the symptoms of patients of previous series presenting focal, non-focal or mixed symptoms.

3. “Where the radiologists blinded to the results of CT? if not, this should be discussed it the limitations of the study.”

Radiologists were blinded to the results of the CT. We added the following chapter under ‘subjects and methods’:

“Neuroradiological images were re-evaluated by three experienced neuroradiologists (L.E., D.M., G.S.-D.). Prior to the reading process, all individual patient data in the
images were replaced by a pseudonomized numeric code. CT and MR images were evaluated in a randomised order. Thus, readers were blinded to the individual CT and MR examinations as well as to the clinical history. After the individual reading process, the participating radiologists met for a consensus reading, leading to a common interpretation of the imaging material.”

4. „If CT was always done prior to MRI, this should be clear in methods, and sequence of the description of technical details accordingly.”

   Please see the comment on 1.) Furthermore, we added a description of the diagnostic work-up in "Material & Methods” as follows:

   “Our institution provides an accredited stroke unit on a 24/7 basis and a TIA outpatient clinic from 8 a.m. to 5 p.m. on weekdays. Standard diagnostic work-up of patients presenting at our hospital with transient neurological episodes is as follows. During the opening hours of our TIA outpatient clinic, immediate MRI examination including FLAIR, DWI, FFE and TOF-MRA sequences is done. If MRI is not available, an unenhanced cranial CT scan and an ultrasound examination of the extra- and intracranial brain-supplying arteries is performed. MRI work-up is completed as soon as possible within 24-72 hours.”

5. „Details of clinical presentation of the series need to be given, such number of transient episodes, duration, and delay from onset to imaging.”

   As suggested, we added number of transient episodes, duration, and delay from last episode to imaging in table 1.

6. „Did all patients with TIA presentation perform MRI during the study period? This would be the only way to draw the conclusion that CT scan is sufficient to detect focal SAH. The design of the study does not allow this conclusion."

   Please see the comment on 1.).

7. „Please change section title 'Introduction' to 'Background'.”

   As requested, we changed section title from "Introduction" to "Background"

8. “Multi-page figures: A figure has been submitted as more than one page. We ask that if a figure consists of multiple parts, a single page should be submitted which contains all parts of the figure. If this is not possible, we recommend that page 1 be submitted as figure 1, page 2 as figure 2, and page 3 as figure 3, etc."

   Figures were formatted as requested.

9. “Copy editing: After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered
further. We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract."

Quality of written English was revised and improved by a professional editing service. We hope it now meets the requirements of BMC Neurology for the quality of written English.

10. “The authors might want to quote another recent series of 17 patients (Apoil et al. Focal Cortical Subarachnoid Hemorrhage Revealed by Recurrent Paresthesias: A Clinico-Radiological Syndrome Strongly Associated with Cerebral Amyloid Angiopathy. Cerebrovasc Dis 2013;36:139–144) in which 15 of 17 CTs were positive vs. 17 MRIs (88%), providing additional evidence that one cannot entirely rely on the CT to rule out a small cortical subarachnoid haemorrhage."

We integrated the case series of Apoil et al. into table 2 and into the results section. Thank you for this substantial reference!

11. „MRI may not be available on a 24/24 basis everywhere, but the CT is sufficient in most cases to get to the diagnosis. The question is: what should the neurologist do in presence of transient neurological symptoms suggesting a focal cortical SAH, and a normal CT? There is a dilemma between not preventing a stroke in a patient with a TIA, and causing an ICH in a patient with amyloid angiopathy. I would not advise antithrombotic treatments knowing that around 10% of patients with cortical focal SAH may have a normal CT. In these rare cases, one cannot escape the need of an MRI. In the meanwhile what can only be expected from the neurologist is to closely monitor the patient and arrange for the MRI to be done as soon as possible.

In our retrospective case series we had no false negative CT-findings for fSAH. We agree that immediate CT scan should be followed by MRI work-up as soon as possible. However, even large stroke centers cannot provide MRI on a 7/24 basis. Thus, unenhanced CT is method of choice to rule out intracranial hemorrhage or brain tumor if MRI is not available.

We integrated your concerns by adding the following sentences to the discussion section:

“One of the most difficult problems that clinicians face in patients with transient neurological deficits, is to avoid misdiagnosis of intracranial haemorrhage as a classical TIA and subsequent mistreatment with antiplatelets or anticoagulants. While early antithrombotic therapy is beneficial in patients with TIA, AHA Stroke Council guidelines recommend “individual assessment of each case” in TIA patients with suspected ICH [12]. The authors cite a “paucity of data from large, prospective, randomized studies” to answer this important management question and emphasize the small number of case series addressing SAH as a potential cause of a TIA-mimic [12].”
12. „The main problem here is that the authors have not predefined a set a priori "gold standard" for detecting fSAH. What were the exact inclusion criteria? How were patients referred and from where? It seems that CT is the most widely used test at their institution in the acute setting, so in fact their gold standard for fSAH in this study is probably an acute CT. Thus their conclusion that CT is 100% sensitive is perhaps not surprising. The ideal study design would probably be for consecutive patients with suspected fSAH (e.g. suspected TIAs, or TIAs with spreading onset), then looking at the yield of CT and the different MRI techniques applied at standardised time points after the onset of symptoms. Could the authors comment on this aspect and clarify how their cases were selected. Could the study be refined to more closely approach the ideal design?“

Patient recruitment and inclusion criteria are now clearly defined in the “Material & Methods” section.

Please refer to our comments 1) and 4) in this letter

13. „As it stands it is difficult to know which population of patients the results can be generalised to, since all those included already had fSAH on CT. In other words the authors do not know how many cases would have been missed by CT if they had routinely done MRI on all suspected cases of fSAH.“

Patient recruitment and inclusion criteria are now clearly defined in the "Material & Methods" section.

Please refer to our comments 1) and 4) in this letter

14. „The previous paper showing that CT did not detect all cases of fSAH is important (Brunot et al, 2010), but suggests that the result seen in the current paper might reflect differences in timing and choice of investigations or population studied. This potential limitation in the interpretation of the findings should be discussed in the paper. “

We fully agree to you and added to following sentence to the discussion section:

“The discrepancy between our results and those in the literature might reflect differences in timing and choice of investigations, which indeed is a notable aspect and might limit our findings. We strongly recommend careful analysis of thin-sliced multiplanar primary reconstruction CT images (ST 0.75 mm / RI 0.5 mm) to enhance investigator-dependent sensitivity for fSAH, and completion of MRI work-up within 3 days.”

15. „Since fSAH is always seems to be seen on FLAIR MRI according to these results, one could also argue that MRI is still the single best test of choice in suspected fSAH as it gives so much information about other manifestations of cerebral small vessel diseases including microbleeds, siderosis as well as ischaemic brain injury and newer small vessel disease markers like perivascular
spaces. Although as the authors state, detecting acute fSAH on CT might be sufficient to want to avoid antithrombotic drugs, the detection of other evidence of cortical siderosis (i.e. a disseminated pattern) seems crucial to assessing the likely future risk of ICH (see Charidimou et al, Neurology 2013) and this still requires MRI.”

In fact! Our aim was not to replace MRI diagnostic by a single unenhanced CT scan. We revised our "Conclusion" as follows:

“According to our data, careful analysis of multiplanar thin-sliced CT allows for detection of acute fSAH with sufficient diagnostic power in an emergency setting. However, despite its appropriateness as a readily available primary diagnostic tool, CT does not provide important additional information about other manifestations of cerebral small vessel diseases, including microbleeds, siderosis, ischaemic brain injury and newer small vessel disease markers. We thus emphasize the need for an extensive secondary MRI work-up which seems to be crucial for assessment of the likely future risk of ICH [15].”

16. “Please clarify timing of CT and MRI in the current series in respect to the clinical events.”

As suggested, we added number of transient episodes, duration, and delay from last episode to imaging in table 1.

17. „The fundamental conclusion that CT is a useful test in suspected TIA is highly controversial given the much higher sensitivity of MRI for small ischaemic as well as haemorrhagic lesions in this clinical setting. A move to a routine recommendation of plain CT in TIA as the authors seem to suggest might be a retrograde step. Can the authors comment on this?“

We fully agree to you, that replacing MRI by CT would be a retrograde step. However we think, that CT diagnostic offers an additional and substantial plus of safety in a setting, when immediate MRI is not available. MRI work-up should be completed as soon as possible.

Please refer also to our comment 15) in this letter