Author's response to reviews

Title: Pyogenic brain abscess, a 15 year survey

Authors:

Jannik Helweg-Larsen (jhelweg@dadlnet.dk)
Arnar Astradsson (arnar.astradsson@gmail.com)
Humeira Richhall (richhall786@yahoo.dk)
Jesper Erdal (erdal@dadlnet.dk)
Alex Laursen (d201790@dadlnet.dk)
Jannick Brennum (jannick.brennum@rh.regionh.dk)

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Pyogenic brain abscess, a 15 year survey.

Jannik Helweg-Larsen, Arnar Astradsson, Humeira Richhall, Jesper Erdal, Alex Laursen and Jannick Brennum

Dear Sir

We appreciate the opportunity to revise our manuscript.

To answer and comply with the reviewer’s comments and suggestions, you will find a careful and detailed response to each of the issues raised by reviewer 2 to 4 in the following.

The reviewers’ comments are written with normal font, our responses are written in italics, deleted text is underlined and added text is in bold.

We believe that this version of the manuscript has been strengthened by the revision and we hope that you will now find it suitable

Yours sincerely

Jannik Helweg-Larsen, MD
Referee 2

1. MAJOR COMPULSORY

a. The main area of controversy/study vis a vis management of brain abscess is the issue of – repeated aspiration or excision.

i. There are data to strongly support each surgical option and the authors should attempt to analyze this aspect of their data in greater detail.

ii. They mention that “In 33 (33%) patients, the primary surgical intervention was followed by repeated aspiration, craniotomy or the insertion of external ventricular drainage.” They also state – “The re-operation rate was significantly higher in patients managed by burr-hole aspiration; 43% underwent a repeat procedure compared to 19% with craniotomy, p=0.05, 95% CI: There was, however, no significant difference between patients managed by burr hole aspiration compared to craniotomy, in the duration of antibiotics or in outcome according to GOS at discharge.” This is difficult to comprehend – would patients who have undergone craniotomy and excision of the abscess with no subsequent recurrence receive antibiotics for the same duration as those who have had multiple sittings of aspiration?

Reply: We agree that this point deserves further exploration. To analyze if the length of treatment had to be prolonged in patients managed by primary aspiration with need for subsequent reoperation compared to patients managed by craniotomy without need for further reoperations,- we have analyzed length of antibiotic treatments (see below). Although we do have data on length of the primary hospital stay this measure is not straightforward to analyze, since several patients were discharged to other rehabilitation units or hospitals for further care. In addition the costs incurred per patient is extremely difficult to analyze retrospectively, why we have refrained from such analysis.

We have added the following section to page 7, duration of antibiotic treatment

There was no difference in the duration of intravenous or total length of antibiotics between patients treated by either burr hole aspiration compared with craniotomy or between patients treated surgically compared with antibiotics only (p=0.34). To compare patients with primary
craniotomy without need of reoperation with patients managed by primary aspiration and subsequent need for reoperations, the length of antibiotic treatments was analyzed; Although the length of postsurgical intravenous antibiotic was somewhat reduced among the 17 patients managed by initial craniotomy without repeat surgical interventions compared to the 29 patients in which primary aspiration were followed by repeat aspiration/operations (median 40 days versus 49 days, p=0.21), the total duration of antibiotic treatment (intravenous and peroral) was comparable (median 76 days versus 70 days, p=0.35).

iii. The authors would also need to mention what their cut-off was with respect to conversion to craniotomy. Would patients who underwent burr hole aspiration and developed recurrence undergo repeated aspirations or would they undergo craniotomy if the lesion recurred after a certain number of aspirations?

iv. Although the outcome and complication rates in these two groups (aspiration and craniotomy) may not have been statistically different in this series, the need to undergo repeated procedures is in itself an undesirable necessity. An analysis of length of hospital stay and costs incurred per patient might have shown some difference between the two groups.

Reply:
In every case possible burr hole aspiration was the preferred primary operation for abscess evacuation and also when repeat evacuation was necessary. In a minority of cases, however, individual surgeon preferences may have dictated the use of a craniotomy instead of burr hole aspiration. Cases where craniotomy was the primary surgical evacuation procedure, included those cases where a neoplasm was initially suspected, warranting a craniotomy, or in the case of postoperative abscess following a craniotomy for intracranial neoplasm or other lesions. Other indications for performing a craniotomy, often dictated in the past, would be if abscess capsule excision was indicated, but we do not usually feel this necessary as penetrance of newer antibiotics is quite good...

The following has been added to Treatments, page 6
The majority of patients, 89%, were treated surgically- table 5. *Burr hole aspiration was the preferred primary operation for abscess evacuation and also when repeat evacuation was necessary. In a minority of cases, however, individual surgeon preferences may have dictated the use of a craniotomy instead of burr hole aspiration. Cases where craniotomy was the primary surgical evacuation procedure, included those cases where a neoplasm was initially suspected, warranting a craniotomy, or in the case of postoperative abscess following a craniotomy for intracranial neoplasm or other lesions.*

Deleted: “The choice of surgical procedure was determined primarily by surgeons’ preference. In general, aspiration was preferred when feasible”

Regarding analysis of analysis of length of hospital stay and costs incurred per patient, please see reply to question i) and ii) above.

2. DISCRETIONARY
   a. The authors are in the unique position of having access to 100% follow-up data. It would have been interesting had they analyzed the long term cognitive outcomes of these patients and compared the patients’ GCS at presentation and the choice of surgical procedure with the long term outcome. This analysis would yield valuable data.

Reply: *We fully agree that more detailed follow-up of cognitive outcomes would be of great interest and do plan to look into this matter in upcoming projects. However, currently, although we have detailed and full follow-up data for all patients regarding mortality, the majority of patients were only followed 6 to 9 months after end of treatment at our departments, why long term cognitive outcomes are not available yet.*

3. MINOR ESSENTIAL –
   a. The authors should also review and include the latest published data about the subject. Some of these references are –


Reply: We appreciate these references and have added the two last suggested references to our discussion (The first reference is not readily available) and now quote the paper by Ratnaike et al directly.

Changed: Discussion, page 10: Recent retrospective studies from East Asia and Europe have reported marked variations in the outcome of brain abscess with mortality rates ranging from 6% to 35% and adverse outcome ranging from 10 to 58%[4-10,14-23]

Added, Discussion, page 13: In a recent retrospective literature review, the mean mortality appeared considerably lower in patients managed by aspiration compared to surgical excision, but did not provide information on measures such as need for reoperation or recurrence[23]. In our series, the need for reoperation was not surprisingly higher in patients managed by aspiration compared to excision, however, the duration of antibiotic treatment was similar.
Reviewer 3

Major comments:

1. The study addresses in a descriptive manner the management of cerebral abscess over 15 years. However, the objectives of the paper namely the identification of delay in management and the outcome are not properly addressed.

Reply: We respectfully disagree. In contrast to other papers on this subject our paper contains detailed data and analysis of delays.

2. The authors report delays due to diagnosis, referral and surgery. However, the factors contributing to each of them and possible reasons for delay in surgery after radiological diagnosis are not clear.

Reply: The reasons for delays are complex, but was most often due to insufficient clinical judgment (not recognizing need for early neuroimaging), insufficient initial imaging (e.g. CT without contrast), interpretation of imaging but also administrative factors such as delays in transportation and the availability of urgent surgery together with other factors. It is clearly difficult within the restriction of this paper to provide a detailed case by case account of the individual 102 patients regarding these matters. However we do believe that we already have provided quite detailed data regarding the possible reasons for delay, please see the section on page 6, Diagnostic Delay and Discussion page 11 to 12.

3. The analysis of outcome in relation to preoperative administration of antibiotics revealed that the outcome of patients receiving antibiotics before surgery compared to patients who first were initiated on treatment at surgery appeared inferior (GOS# 3, 33% vs 11%, p=0.011). The authors state that, there was, however, no association between outcome and administration of pre-surgical antibiotics when adjusted for CRP at admission. The authors have not demonstrated the effect of CRP levels in outcome in the first place and have not explained further why a correction for CRP was considered.
Reply: We agree that the section on CRP adjustment is not clear. Our analysis of outcome, initiation of antibiotics and CRP was done to more fully adjust for the presence of severe infection at admission, as such patients would be more likely to receive antibiotics before surgery in contrast to patients presenting without features of concurrent infection or sepsis.

To more fully describe the background, we have added the following section to Outcome, page 9:

“Administration of empirical antibiotics before surgery was initiated in 36 of 89 (40%) patients. Overall, the outcome of patients receiving antibiotics before surgery compared to patients who first were initiated on treatment at surgery appeared inferior (GOS≤ 3, 33% vs 11%, p=0.011). However, since the decision to administer antibiotics before operation and outcome was critically influenced by presence of severe infection at admission, which would be reflected in an elevated CRP, outcome was reanalyzed according to CRP at admission. The outcome of patients with elevated admission CRP (> 20 mg/l) was inferior to patients presenting with a normal CRP (GOS≤ 3 29% vs 7%, p=0.025). No association between outcome and administration of pre-surgical antibiotics was found when adjusted for CRP at admission. “

4. The study can be strengthened by attempting to identify the trends in incidence and management over the study period of 15 years.

Reply: This is obviously of interest and we did look at this issue in detail in our initial analysis (not presented). However, although 15 years may seem a long time, the number of patients admitted with brain abscess was relatively limited each year. Overall we found no clear trend for differences in the incidence or clear evidence for changes in the management over the study period.

Minor comments:
The study lacks in clarity in a number of features on management namely the decision making on craniotomy/ aspiration; continuation of antibiotics; use of steroids. These can be explained by the retrospective nature of the study; however, it weakens the study.
Reply: Please see response to referee 2.

The authors should discuss the reasons for providing antibiotics for less than 6 weeks in a cohort of patients, while continuing the same for a longer time in others. As mentioned by the authors, it does not appear to be related to the excision of the abscess.

Reply: The reasons for providing antibiotics for less than 6 weeks were at the discretion of the treating physician. In the absence of solid evidence for prolongation of treatment, several clinician may opt for shorter treatment in patients with sufficient response. This fact is already mentioned at page 4, quote “The choice and length of antibiotic treatment were not uniform; changes in treatments were common, based on individual microbial findings, tolerability and/or the treating physicians’ preferences”.
Reviewer 4

Minor Essential Revisions

1. There are a lot of spelling mistakes such as metronidazol (page 3), clindamycine, vancomycine, cephalosporine (page 7 and others), succes (page 11)

*Reply: We apologize, these error have now been corrected.*

2. There are some inconsistent words e.g. burrhole vs burr-hole (page 7,8), brain abscess vs cerebral abscess vs cerebral abscess vs intracerebral abscess in the same article.

*Reply: To be consistent we now almost uniformly use the word “brain abscess” and “burr hole” in the text.*

3. Wrong word: (<1.000 cells/μl) pleocytosis. Did you mean (<1,000 cells/μl) pleocytosis?

*Reply: Corrected to (<1000 cells/μl)*

4. There is no description of the last figure.

*Reply: There is already a legend for figure 1 and the figure is referred in the text.*