PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality following a brain tumour diagnosis in multiple sclerosis patients
AUTHORS	Montgomery, Scott; Hassan, Ahmad; Bahmanyar, Shahram; Brus, Ole; Hussein, Oula; Hiyoshi, Ayako; Hillert, Jan; Olsson, Tomas; Fall, Katja

VERSION 1 - REVIEW

REVIEWER	Professor & Head of Research Egon Stenager Institute of Regional Health Research, University of Southern Denmark & Hospitals of Southern Jutland, Denmark No competing interests.
REVIEW RETURNED	26-Aug-2013

THE STUDY	1) In article summary the authors focus on whether or not brain tumour treatment worsen MS progression. The study does not give an answer to this question. 2) It should be stated how many were MS patients among the excluded 479 persons (due to missing information). 3) In article summary it is stated that the majority of MS patients with brain tumours were included. What was the majority in percentage? 4) The text reports that a minority of the MS patients were not matched with 12 controls. The abstract state that all MS patients were matched? 5) Immunomodulatory treatment (yes/no) may be a confounder. Is this information in the register? 6) Does the register include information on numbers of MRI scans before tumour diagnosis in MS patients? 7) reference 2: pages is 614-15 - not 614-6 8) website for reference 3? 9) Apparently, the cohort in reference (paper) 1 is the same as in this paper. However, the numbers of included persons differ. Explain, please.
RESULTS & CONCLUSIONS	1) We do not get an answer to whether or not brain tumour treatment may worsen MS progression 2) Tumour diagnosis at an earlier age in MS patients: could MS pathology provoke earlier onset af tumour pathology?
GENERAL COMMENTS	Nice study which add new information to previous studies on this subject. A little more information and discussion may be of benefit for the readers and peers.

REVIEWER	Filipe Palavra, MD Multiple Sclerosis Centre of Catalonia (Cemcat) Vall d'Hebron University Hospital

	Barcelona Spain I declare no competing interests.
REVIEW RETURNED	18-Sep-2013

THE STUDY	The level of written English is adequate for publication, but I should suggest to the authors a minor review/polish of the text.
GENERAL COMMENTS	1. Types of tumours diagnosed among MS patients should be clearly stated in "Results" and not only considered in Table 1 legend. These are relevant data considering the message authors are conveying and deserve to be highlighted in the manuscript. 2. Spinal cord tumours were excluded from the analysis, but it would be interesting to explain if there are (or not) such diagnoses among patients included in the database and, if considering those diagnoses, some changes would be produced in the final results. Would they have any significant impact on MS patients' prognosis and mortality? 3. It would be interesting to provide data on MS clinical phenotypes when the diagnosis of brain tumour was made (at least a separation between relapsing and progressive forms could be extremely useful in clinical grounds). Could this variable introduce any change in the regression model used? 4. MS specific treatments can also have an impact on prognosis and mortality among patients diagnosed with brain tumours. Does this variable have any impact on the statistical model used? 5. On page 11, line 36 (Table 1, column 2), a parenthesis is lacking prior to "18.0)". 6. None of the authors is linked with the affiliation number 4 (Clinical Research Centre, Golestan University of Medical Sciences, Gorgan, Iran). This needs to be revised.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Professor & Head of Research
Egon Stenager

Institute of Regional Health Research, University of Southern Denmark & Hospitals of Southern Jutland, Denmark

No competing interests.

1) In article summary the authors focus on whether or not brain tumour treatment worsen MS progression. The study does not give an answer to this question.
AUTHORS' RESPONSE: The focus of the article was intended to be whether brain tumours had a worse prognosis (in terms of mortality) in MS patients. One putative mechanism that may underlie this (although there are others) is through changes in disease course. We did not intend, nor are we able, to measure disease course using these data. The main outcome (mortality) has now been more clearly identified in the introduction and discussion sections of the paper.

2) It should be stated how many were MS patients among the excluded 479 persons (due to missing information).

AUTHORS' RESPONSE: This information has now been added to the manuscript: 267 with MS and 212 without were excluded from the larger original cohorts.
3) In article summary it is stated that the majority of MS patients with brain tumours were included. What was the majority in percentage?
AUTHORS' RESPONSE: The Cancer Register is very complete (over 99%) in terms of cancer diagnoses. Up until 2001, the MS diagnoses from the Patient Register required a hospital admission, so it is possible that some individuals with MS would not have been identified. However, almost everyone with a brain tumour diagnosis would be admitted to hospital and a pre-existing diagnosis of MS is likely to have been recorded at that point, resulting in inclusion in our MS cohort. While we cannot provide an exact percentage, we believe that the study will have identified the majority of MS patients with a brain tumour during the study period. This information has been added to the text of the discussion section.

4) The text reports that a minority of the MS patients were not matched with 12 controls. The abstract state that all MS patients were matched?
AUTHORS' RESPONSE: This has been corrected in the abstract as the actual numbers are reported instead.
5) Immunomodulatory treatment (yes/no) may be a confounder. Is this information in the register?
AUTHORS' RESPONSE: Unfortunately, this information is not available in these data. However, we have added truncation by calendar period (before the introduction period of interferon-beta) to investigate this possible influence and augmented the discussion section accordingly. While we do not know who was exposed in the latter period (usage was far from for the majority when interferon-beta was first introduced), making analysis unfeasible, there will have been no notable exposure before 1996 – so our truncated analysis is justified.

6) Does the register include information on numbers of MRI scans before tumour diagnosis in MS patients?
AUTHORS' RESPONSE: Unfortunately, the quality of MRI data is not sufficiently high in this dataset and its use could introduce selection bias. We now comment on this limitation in the discussion.
7) reference 2: pages is 614-15 - not 614-6
AUTHORS' RESPONSE: This has been corrected
8) website for reference 3?
AUTHORS' RESPONSE: This has been corrected

9) Apparently, the cohort in reference (paper) 1 is the same as in this paper. However, the numbers of included persons differ. Explain, please.
AUTHORS' RESPONSE: The current paper is limited to subjects with brain tumours, whereas the earlier study sought to identify all those with an MS diagnosis and matched them with a comparison cohort from the general population. This has been further clarified in the text of the introduction section.
1) We do not get an answer to whether or not brain tumour treatment may worsen MS progression

AUTHORS' RESPONSE: The focus of the article was intended to be whether brain tumours had a worse prognosis (mortality) in MS patients. One putative mechanism that may underlie this (although there are others) is through changes in disease course. We did not intend, nor are able, to measure disease course using these data. The main outcome (mortality) has now been more clearly identified throughout the text.

2) Tumour diagnosis at an earlier age in MS patients: could MS pathology provoke earlier onset af tumour pathology?

AUTHORS' RESPONSE: This is a reasonable assertion and has been added to the manuscript as a

possible explanation. While it could be argued that the higher proportion of less aggressive tumour types among MS patients could suggest a surveillance effect, earlier onset may also remain a possibility. Despite this, the main clinical question is whether mortality is raised in MS patients after age has been taken into account (and mortality is not raised). This has now been explicitly covered in the discussion section.

Nice study which add new information to previous studies on this subject. A little more information and discussion may be of benefit for the readers and peers.
AUTHORS' RESPONSE: Thank you

Reviewer: Filipe Palavra, MD
Multiple Sclerosis Centre of Catalonia (Cemcat) Vall d'Hebron University Hospital Barcelona Spain

I declare no competing interests.

The level of written English is adequate for publication, but I should suggest to the authors a minor review/polish of the text.
AUTHORS' RESPONSE: The English has been reviewed and -hopefully- improved.

1. Types of tumours diagnosed among MS patients should be clearly stated in "Results" and not only considered in Table 1 legend. These are relevant data considering the message authors are conveying and deserve to be highlighted in the manuscript.
AUTHORS' RESPONSE: More detailed information on tumour type is now provided and discussed (although as some of these data were previous reported in published correspondence, the discussion is limited to avoid repeat publication).

2. Spinal cord tumours were excluded from the analysis, but it would be interesting to explain if there are (or not) such diagnoses among patients included in the database and, if considering those diagnoses, some changes would be produced in the final results. Would they have any significant impact on MS patients' prognosis and mortality?
AUTHORS' RESPONSE: All patients with primary brain tumours were included (even if potentially with spinal cord involvement). In fact, none of patients with a primary brain tumour had a contemporaneous diagnosis of a spinal tumour (even though a small number had a second diagnosis some years later). We have now conducted a sub-analysis that adds those with primary spinal cord tumours and this has resulted in additions to the methods, results and discussion sections of the paper. There was no evidence of a worse outcome when the additional patients were included.

3. It would be interesting to provide data on MS clinical phenotypes when the diagnosis of brain tumour was made (at least a separation between relapsing and progressive forms could be extremely useful in clinical grounds). Could this variable introduce any change in the regression model used?
AUTHORS' RESPONSE: We agree that this would be very interesting, but unfortunately phenotype data at cancer diagnosis are unavailable for the vast majority of MS patients in this study. We now mention this limitation explicitly. Future studies will be able to make use of phenotype data from the MS Register, which had not been established for a sufficient duration of the study period reported here.

4. MS specific treatments can also have an impact on prognosis and mortality among patients diagnosed with brain tumours. Does this variable have any impact on the statistical model used?
AUTHORS' RESPONSE: Unfortunately, information on pharmaceutical treatment is not available for these data as they pre-date the Swedish Prescription Register. However, we have added stratification

by time period to investigate possible treatment influences and augmented the discussion section accordingly (see above).
5. On page 11, line 36 (Table 1, column 2), a parenthesis is lacking prior to “18.0)”.
AUTHORS’ RESPONSE: This has been corrected
6. None of the authors is linked with the affiliation number 4 (Clinical Research Centre, Golestan University of Medical Sciences, Gorgan, Iran). This needs to be revised.
AUTHORS’ RESPONSE: This has been corrected.