PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis
AUTHORS	Granberg, Tobias; Martola, Juha; Aspelin, Peter; Kristoffersen Wiberg, Maria; Fredrikson, Sten

VERSION 1 - REVIEW

REVIEWER	Lebrun-Frenay, Christine Department of Neurology of Nice University, neurology
REVIEW RETURNED	14-Aug-2013

GENERAL COMMENTS	The manuscript is very clear and well-written. This introduction is a good review about RIS. Minor suggestions are proposed in the pdf.

- The reviewer also provided a marked copy with highlighted changes which is available upon request.

REVIEWER	Jesper Hagemeier Senior Biostatistician and Research Scientist Buffalo Neuroimaging Analysis Center, Department of Neurology, University at Buffalo, NY, USA I have no potential conflicts of interest or disclosures to report.
REVIEW RETURNED	19-Sep-2013

THE STUDY	No Supplemental documents.
GENERAL COMMENTS	“Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis” is an interesting retrospective study incorporating all scans done for a year (2001) in a tertiary referral hospital in Sweden. It is a thorough, clear and relevant manuscript, which proposes that the occurrence of RIS using new, strict, criteria, is in fact rare. Results are interesting, but will have to be interpreted in the context of referred patients, not healthy subjects. Limitations (such as patient drop-out) are generally well described. Minor comments:

	Comment 1: In the introduction, 2nd paragraph, several studies are mentioned, but not explicitly cited. The Giorgio citation is not present in the reference list, are the authors referring to Stromillo et al? Comment 2: The authors state that “This suggests that RIS in some cases may be considered to be preclinical MS.” It would be helpful if clinically isolated syndrome was also addressed in the discussion, and how it may relate to RIS in this sample, if this was investigated. Comment 3: The study aim is to identify RIS patients in a tertiary hospital setting and depict long-term prognosis. However, it is unclear what is meant by “long-term prognosis”. It should be clarified what (quantitative) measures are used to determine long-term prognosis (in addition to the case study) Comment 4: The biggest limitation of the study is probably the make-up of the sample. Ideally all subjects would be recruited from the healthy, normal population. However, all subjects were already referred to the specialist hospital settings, and therefore, neurological findings are relatively common. However, according to the used (stringent) Okuda criteria still only 1 subject with RIS was identified, who within 3 months converted to multiple sclerosis. Even though nowhere in the manuscript it is claimed that the population is comprised on healthy controls, it would be advisable to stress this fact as a limitation, as it influences the interpretation of the study, as well as generalizability to the general population. For example, it is proclaimed several times that there was an incidence of RIS of 1 in 2105, but this is “incidence” is in the referred population, not the general population. Therefore, the main message of this manuscript remains (should be) that the occurrence of RIS using current criteria is rare, even in a population of (likely) neurological patients. Perhaps the authors could comment on the why RIS incidence was so exceptionally low in relation to this specific tertiary hospital sample. One would expect slightly higher incidence because of this. For example, in a recent study (should be cited) by Gabelic et al 2013 (AJNR doi: 10.3174/ajnr.A3653), in a much smaller sample of authentic healthy subjects, 4 people (out of 150) satisfied Okuda criteria for RIS.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 – Christine Lebrun
Statement 1: The manuscript is very clear and well-written. There is in the introduction a good review about RIS.

Response: Thank you for your kind words.

Comment 1: For RIS with cognitive symptoms, it is important to precise the difficulties to differentiate them from cognitive forms of MS.

Response: We thank you for your comment and agree with it. The main difference from our perspective is that MS with mainly cognitive symptoms, such as described by Staff and colleagues in 2009 (doi: 10.1001/archneurol.2009.190), usually is accompanied by other symptoms that lead to the suspicion, and diagnosis, of MS. These patients would thus by definition not fulfil the RIS criteria. In terms of the similarities of the cognitive test profiles, we believe that they are out of scope for this article. We have however covered it quite extensively in a recent systematic review (doi: 10.1177/1352458512451943).

Comment 2: The actual criteria define patients with 3/4 Barkhof criteria as RIS and RIS patients with DIT as RIS at high risk for converting in MS.

Response: Thank you for your comment. It is true that the Okuda A2 criterion requires a fulfilment of at least 3 out of 4 Barkhof criteria and that patients with a radiologically demonstrated DIT are at high risk of clinical conversion to CIS/MS. We have previously covered this and other currently known predictors in the aforementioned review. Interestingly, the risk for clinical conversion after radiological demonstration of DIT was also true in the specific case outlined in our manuscript.

Comment 3: It could be useful to add Gabelic et al: "Prevalence of Radiologically Isolated Syndrome and White Matter Signal Abnormalities in Healthy Relatives of Multiple Sclerosis Patients".

Response: Thank you for your suggestion. The reference in question was published after the drafting of the manuscript but is of course highly relevant to this study why it is now cited in the sixth paragraph of the Introduction and implemented in a new second paragraph of the Discussion.

Reviewer 2 - Jesper Hagemeier
Statement 1: "'Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis' is an interesting retrospective study incorporating all scans done for a year (2001) in a tertiary referral hospital in Sweden. It is a thorough, clear and relevant manuscript, which proposes that the occurrence of RIS using new, strict, criteria, is in fact rare. Results are interesting, but will have to be interpreted in the context of referred patients, not healthy subjects. Limitations (such as patient drop-out) are generally well described."

Response: Thank you for your kind words.

Comment 1: In the introduction, 2nd paragraph, several studies are mentioned, but not explicitly cited. The Giorgio citation is not present in the reference list, are the authors referring to Stromillo et al?

Response: Thank you for your comment that made us aware of that the above-mentioned sentence is not specific enough in terms of which citations are referred to. The mentioning of Giorgio's name referred to both the work in the Stromillo citation, but also the work in several of the studies from the Italian groups where Giorgio's name appears in the later parts of the author lists. In order to reduce

the risk of misunderstandings, we have chosen to remove the specific names and instead let the citations speak for themselves.

Comment 2: The authors state that “This suggests that RIS in some cases may be considered to be preclinical MS.” It would be helpful if clinically isolated syndrome was also addressed in the discussion, and how it may relate to RIS in this sample, if this was investigated.

Response: Thank you for your comment. In this study we aimed to identify any patients with RIS in the sample regardless of whether remained stable or converted to CIS/CDMS. How RIS relates to CIS has been discussed in several reviews and editorials in recent years. It is an interesting topic, but it also something we believe is out of scope for this manuscript why we have chosen not to introduce that discussion in the manuscript.

Comment 3: The study aim is to identify RIS patients in a tertiary hospital setting and depict long-term prognosis. However, it is unclear what is meant by “long-term prognosis”. It should be clarified what (quantitative) measures are used to determine long-term prognosis (in addition to the case study)

Response: Thank you for your comment. We have now clarified that the long-term prognosis in this retrospective study is constituted by the 11 years past between the sample year (2001) and the year the study was conducted (2012). This clarification has been added in the first paragraph of the Methods section and in the third paragraph of the Discussion.

Comment 4: The biggest limitation of the study is probably the make-up of the sample. Ideally all subjects would be recruited from the healthy, normal population. However, all subjects were already referred to the specialist hospital settings, and therefore, neurological findings are relatively common. However, according to the used (stringent) Okuda criteria still only 1 subject with RIS was identified, who within 3 months converted to multiple sclerosis.

Response: Thank you for your comment. Although the hospital-based sample is a limitation in terms of the generalizability of the results to the ‘healthy’ general population, the sample was actually chosen in order to determine the hospital-based prevalence of RIS in accordance with the study conducted in Pakistan by Wasay and colleagues (doi: 10.1136/jnnp.2009.180000).

Statement 2: “Even though nowhere in the manuscript it is claimed that the population is comprised on healthy controls, it would be advisable to stress this fact as a limitation, as it influences the interpretation of the study, as well as generalizability to the general population. For example, it is proclaimed several times that there was an incidence of RIS of 1 in 2105, but this is “incidence” is in the referred population, not the general population. Therefore, the main message of this manuscript remains (should be) that the occurrence of RIS using current criteria is rare, even in a population of (likely) neurological patients.”

Response: Thank you for your comment. If this study had aimed to determine the prevalence of RIS in the general public, this sampling method would of course be extremely biased. This study did, however, aim to determine the frequency of RIS findings in this tertiary hospital setting. In order to clarify that the sample is not population-based, the word ‘hospital’ has been added to the phrase ‘tertiary setting’ (i.e. tertiary hospital setting) in both the Abstract, the Article Summary and the Discussion.

Statement 3: Perhaps the authors could comment on the why RIS incidence was so exceptionally low in relation to this specific tertiary hospital sample. One would expect slightly higher incidence because of this. For example, in a recent study (should be cited) by Gabelic et al 2013 (AJNR doi: 10.3174/ajnr.A3653), in a much smaller sample of authentic healthy subjects, 4 people (out of 150)

satisfied Okuda criteria for RIS.

Response: The reasons for the low prevalence of RIS in this particular sample have been extensively considered in the Discussion. The reference in question was published after the drafting of the manuscript but is of course highly relevant to this study why it is now cited in the sixth paragraph of the Introduction and implemented in a new second paragraph of the Discussion. Although your results are very interesting in the RIS field in general the comparability to this study is limited due to differences in the aims and methodologies of the studies.

We hope that these revisions and clarifications are of satisfaction to the editors and the reviewers.