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Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis

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ABSTRACT

Objective: The improved availability of magnetic resonance imaging (MRI) in medicine has led to an increase in incidental findings. Unexpected brain MRI findings suggestive of multiple sclerosis (MS) without typical symptoms of MS were recently defined as radiologically isolated syndrome (RIS). The prevalence of RIS is uncertain. The aim of this study was to determine the prevalence of RIS at a university hospital in a ~~country~~ region with a high prevalence for MS and describe the long-term prognosis of the identified patients.

Design: Retrospective cohort study conducted in 2012.

Setting: All brain MRI examinations performed at Karolinska University Hospital in Huddinge, Stockholm, Sweden during 2001 were retrospectively screened by a single rater for findings fulfilling the Okuda criteria. The sample year was chosen in order to establish the long-term prognosis of the patients identified. The examinations of interest were re-evaluated according to the Barkhof criteria by a neuroradiologist with long experience in MS.

Participants: In total 2105 individuals were included in the study. Ages ranged from 0 to 90 years with a median age of 48 years. Only one patient with RIS was identified, equivalent to a prevalence of 0·05% in the studied population, or 0·15% among patients aged 15 to 40 years. The patient with RIS developed symptoms consistent with MS within three months accompanied with radiological progression and was diagnosed with MS.

Conclusions: RIS, according to present criteria, is an uncommon finding in a tertiary setting in a high-prevalence ~~country~~ region for MS where awareness and clinical suspicion of MS is common. In order to study the prognosis of RIS, multi-center studies, or case-control studies are recommended.

Comment [TG1]: The abstract has been restructured according to BMJ Open standards

ARTICLE SUMMARY

Article focus

- Incidental magnetic resonance imaging findings suggestive of multiple sclerosis in patients without typical symptoms of demyelinating disease is called Radiologically Isolated Syndrome and poses a clinical dilemma for physicians.
- The aim of this study was to investigate the prevalence of the newly defined Radiologically Isolated Syndrome at a university clinic in Stockholm, Sweden.

Key messages

- Radiologically Isolated Syndrome was an uncommon finding, and was identified only in 1 out of 2105 examined individuals (0.05 %).
- The patient rapidly progressed radiologically and clinically to multiple sclerosis.

Strengths and limitations of this study

- This is the first study reporting on the frequency of Radiologically Isolated Syndrome in a high-prevalence region for multiple sclerosis.
- The study was a systematic re-evaluation of a yearly sample at a large university clinic.
- The retrospective nature of the study gives the possibility to report on the long-term prognosis for the patients, but also gives rise to losses to follow-up.
- The generalizability of the results to non-tertiary settings and to regions with a lower

prevalence of multiple sclerosis is limited.

INTRODUCTION

Magnetic resonance imaging (MRI) has revolutionised our ability to image the central nervous system and it has become readily accessible in clinical practice. With the improved availability and sensitivity of MRI there is an increase in incidental findings.[1] In 2009, Okuda and colleagues defined incidental MRI findings suggestive of multiple sclerosis (MS) without typical MS symptoms as Radiologically Isolated Syndrome (RIS).[2] This has led to an increased awareness of this condition and a convergence in terminology.[3]

Since the definition of RIS, studies by Lebrun, Okuda, de Stefano, Amato, Siva, Giorgio, and their colleagues have been especially important in showing that there is a close association between RIS and MS. Patients with RIS often have a subclinical cognitive impairment with a similar test profile of deficits compared to patients with MS.[4–6] The association of RIS and MS is also strengthened in that both patient groups show similarities in both qualitative and quantitative MRI measurements.[6–8] There are case reports with follow-ups of up to 10 years,[4,9,10] and the range of mean follow-up times in the published cohorts are 2·4 to 7 years.[2,11–17] These studies show that roughly two-thirds progress radiologically and one-third develop clinical symptoms, and thereby convert to clinically isolated syndrome or MS, during their follow-up times.[3] This suggests that RIS in some cases may be considered to be preclinical MS. The patients with RIS is therefore of particular interest to study in a pathophysiological aspect since it may shed light on early changes that precedes the onset of classical MS symptoms.

Headache is the most common reason for performing the initial MRI unveiling RIS, but it is unclear if there is a causative relationship between the incidental MRI findings and the headaches.[3] Recently a study by Liu and colleagues showed that among patients undergoing a

MRI of the brain due to headaches, MRI findings fulfilling the Barkhof criteria are common. Depending on the definition of juxtacortical and periventricular, 2·4–7·1% of the patients fulfilled the Barkhof criteria.[18]

~~Although RIS is a newly defined entity,~~ Incidental MS findings are previously known from ~~previous anatomo pathological~~autopsy studies from the late 20th century indicating~~performed in the 1960s to the 1990s in Europe and North America.[4–7] As a systematic review of RIS recently concluded, these studies with 2,450 to 15,644 patients indicated~~ a frequency of unexpected post-mortem MS findings in the range of 0·08–0·2%.[19–22] ~~It is, however, hard to interpret what relevance these results have today with the reported increase of MS incidence and prevalence in many regions.[3]~~

The incidence and prevalence of the newly defined RIS is, however, currently unknown.[3] In 2009 Morris and colleagues published a meta-analysis of 16 studies including 15,559 healthy control subjects that reported nine cases of "definite demyelination" and four cases of "possible demyelination" corresponding to a frequency of 0·06% and 0·03% respectively.[1] There is unfortunately no report on the clinical history or neurological examination of these cases why the results cannot be assumed to reflect RIS. Instead the results of five original articles, identified as the most relevant, are described below.

An American study published in 1996, described 23 patients with MRI findings highly suggestive of MS (according to Paty's classification) in a population of 2,783 psychiatric patients. However, 13 patients had neurological symptoms that were not further specified, which gives a possible asymptomatic frequency of roughly 0·4%. It is unknown if these patients had any neurological findings that would exclude them from a RIS diagnosis.[23] The results are nonetheless interesting since psychiatric symptoms have frequently been reported

as the original indication for performing the MRI examination that unveiled the RIS.[3] A second American study published in 1999 showed that among 1,000 asymptomatic subjects, there where three persons (0·3%) with findings classified as possible demyelinating disease.[24] A German study published in 2006 described a cohort of 2,536 young male military recruits in which one person (0·04%) had findings suggestive of demyelinating disease, but it is not specified if this person had any neurological symptoms or findings.[25] A second German study was published in 2010, which showed that of 206 healthy young volunteers two (1·0%) had multiple white matter lesions, but it is unclear whether the findings fulfilled the Barkhof criteria.[26]

The only study reporting on the frequency of RIS since its definition comes from a hospital based study ~~The latest MRI study, performed~~ in Pakistan published in 2011. It revealed that out of 864 persons in the ages 15 to 40 years there were six cases (0·7%) of incidental MRI findings suggestive of MS in patients without relapsing neurological symptoms or pathological neurological findings.[27] This last study reports a surprisingly high frequency of such findings in a region reported to have a low prevalence of MS (<5 per 100,000 population).[28] In comparison the estimated prevalence of MS in Sweden, where the present study was conducted, is 189 per 100,000 population.[29] In conclusion there has not been any study reporting on the prevalence of RIS in a high-prevalence region for MS since the definition of RIS.

This study aims to clarify in what frequency RIS findings can be expected in a tertiary hospital setting in a high-prevalence ~~country~~ region for MS and depict the long-term prognosis of RIS in the patients identified.

METHODS

Study population and ethical approval

The study sample in this retrospective study conducted in 2012 is based on the digital radiological information system and digital patient charts at Karolinska University Hospital, Huddinge (formerly Huddinge University Hospital), Stockholm, Sweden. The hospital is a tertiary referral hospital for the greater southern Stockholm area with a population of 800,000 inhabitants. In order to establish the long-term prognosis of the patients identified the sample year was chosen to 2001, when both the patient charts and the radiological data were fully digitalised. All persons undergoing a brain MRI at the hospital during the sample year were included in the study. The study was approved by the regional ethical review board in Stockholm at Karolinska Institutet, which allowed a general screening of the examinations described above, and written informed consent was obtained according to the approval in those cases where more information was necessary through access of the clinical patient charts.

Screening method

The screening of the study population was made systematically by one physician at the radiology department with previous experience of radiological research (TG). All documentation from the MRI examinations from 2001 was available to the screener and read to full extent. The material included both the query, the clinical information in the referral (clinical history, symptoms, and findings) as well as the radiological findings according to the regular clinical radiological assessment.

MRI examinations

All MRI examinations were performed in the regular clinical setting in one of two 1·5 T MRI machines, Siemens Magnetom Vision and Symphony (Siemens Medical Systems GmbH, Erlangen, Germany). The MRI examinations were performed according to standard clinical

protocols depending on the original clinical query and white matter anomalies were in most cases further characterised with the standardised MS MRI protocol used at the clinic described in Table 1.

Table 1

MRI parameters of the standardised MS protocol

Sequence	Plane	SLT (mm)	TR (ms)	TE (ms)	TI (ms)	FA (°)
T1 MPRAGE	Axial	1·5	13·5	7	300	15
PD TSE	Axial	3·0	4761	22	-	180
T2 TSE	Axial	3·0	4761	90	-	180
T2 TSE*	Sagittal	4·0	3500	96	-	180
FLAIR*	Axial	5·0	9000	110	2500	180
T1 SE*	Axial	5·0	570	14	-	90

*Acquired post-gadolinium-DTPA contrast media.
FA, flip angle; FLAIR, fluid attenuated inversion recovery; MPRAGE, three-dimensional magnetization prepared rapid acquisition gradient echo; PD, proton density; SE, spin echo; SLT, slice thickness; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo.

Radiological assessment

All examinations had been reviewed, signed, and contra-signed as part of the regular clinical radiological routine. At least one of the clinical reviewers was a specialist in neuroradiology. The examinations identified with possible RIS findings in the screening process were re-evaluated according to the Barkhof criteria by another neuroradiologist (JM) with long experience of classifying MS-like findings.

Clinical assessment

The referring doctor conducted the initial clinical assessments. All patients that were identified as possible RIS cases in the screening had been examined by a neurologists as part of the following clinical investigation. All patients diagnosed with MS received their diagnosis according to contemporaneous diagnostic criteria after careful investigation lead by a neurologist with experience of MS.

RESULTS

Prevalence of RIS

During the year of 2001 a total of 2105 individuals had at least one MRI examination of the brain at Karolinska University Hospital in Huddinge, Stockholm, Sweden. Among the patients there were 903 men (43%) and 1202 women (57%) with an age span of 0 to 90 years with 669 persons being between 15 and 40 years of age. Mean age was 46·2 years and median age was 48 years. The following results are also schematically described in Figure 1. Out of all patients 542 had normal findings. The spectrum of findings is presented in Table 2. Common findings besides white matter changes were tumours, atrophy, infarctions, and sinusitis.

Table 2

Overview of MRI findings (n)

Within normal limits	**542**
Cerebrovascular disorders	**326**
- Aneurysm	8
- Carotid dissection or occlusion	12
- Cavernous malformation	19
- Cerebral contusions	4
- Cortical infarction	89
- Developmental venous anomaly	29
- Lacunar infarction	133
- Intracerebral haemorrhage	15
- Cerebral venous sinus thrombosis	5
- Subarachnoid haemorrhage	3
- Subdural hematoma or hygroma	6
- Other	3
White matter and neurodegenerative disorders	**1143**
- Atrophy	285
- Basal ganglia disorders	12
- Hydrocefalus	20
- Marked perivascular spaces	37

- Possibly inflammatory white matter changes	356
- Unspecific or degenerative white matter changes	433
Infectious, inflammatory and metabolic disorders	**88**
- Cerebral abscess	7
- Congenital metabolic disorders	4
- Encephalitis	10
- Meningitis	15
- Optical neuritis	37
- Vasculitis	4
- Other	11
Neoplasms	**311**
- Acoustic neuroma	19
- Glioma	21
- Meningioma	44
- Metastasis	18
- Pituitary adenoma	31
- Unspecified or other type of neoplasm	46
Cysts and malformations	**74**
- Arachnoid cyst	24
- Empty sella	9
- Malformation or dysplasia	16
- Parenchymal cyst	5
- Pineal cyst	13
- Pituitary cyst	7
Sinonasal and orbital disorders	**191**
- Sinusitis	164
- Mastoiditis	23
- Other	4

In total 789 patients had white matter anomalies (not involving those caused by other diseases). Out of these patients, 433 had unspecific white matter changes that did not fulfil the Barkhof criteria (solitary findings) or had a more likely explanation; such as an ischemic-degenerative pattern in elderly and/or patients with known severe cardiovascular disease. Out of the 356 patients with white matter changes possibly reflecting demyelinating disease, 158

patients were known to have MS and 6 received their MS diagnosis as part of the investigation in question. Out of the 192 remaining patients 139 were reported to have apparent neurological symptoms in the referral that would exclude the findings from being classified as RIS according to the B criteria in the Okuda classification, but where it was unclear if they had already gotten a diagnosis of Clinically Isolated Syndrome or MS. After this screening only 53 patients remained with findings that were plausible RIS but where more clinical information was needed. In compliance with the ethical approval these patients were asked for written informed consent in order for us to evaluate their clinical patient charts.

Of these 53 patients where further information was needed, 3 patients were deceased, 7 did not respond and 4 declined participation. The patient charts of the remaining 39 persons that gave their informed consent were then examined in order to better understand the patients' clinical history, symptoms and neurological findings. This additional information revealed that 21 had been diagnosed with MS. Another 12 had intermittent clinical symptoms dismissing a RIS classification, presented in Table 3, but where the patients had not yet received a diagnosis of MS. In 3 cases there was insufficient clinical data to draw a conclusion. ~~(such as hemidysesthesia, Lhermitte's sign, diplopia, and ataxia) and in 3 cases there was insufficient clinical data to draw a conclusion.~~ In the end, 3 patients with plausible RIS remained and after neuroradiological assessment 1 patient was classified as having RIS. This is equivalent to a prevalence of 0·05% in the studied population and 0·15% among the patients in the ages of 15 to 40 years.

Table 3

Presenting symptoms in the 12 patients not classified as RIS

Comment [TG2]: Table 3 is a new addition to this manuscript

Sex	Age (years)	Symptoms
F	25	Optical neuritis, Lhermitte's sign
F	26	Diplopia, hemiparesis
F	39	Optical neuritis, facial hemidysesthesia
F	43	Optical neuritis
F	47	Recurrent hemidysesthesia
F	58	Trigeminal neuralgia
F	62	Hemidysesthesia, facial paralysis
F	62	Hemidysesthesia
M	18	Severe vertigo, ataxia
M	18	Lhermitte's sign
M	27	Diplopia, vertigo, dysesthesia
M	44	Hypesthesia

F, female; M, male.

Case description

The patient with RIS was a 43 year-old woman without any neurological symptoms or any history of neurological disorders except for migraine since more than 10 years. A neurological examination did not reveal any pathological findings. She had good effect of triptanes. Due to her long history of migraine and still frequent attacks she was referred for a MRI of the brain in February of 2001. The scan showed 15 supratentorial T2 lesions, out of which 12 were periventricular and 2 were juxtacortical. Gadolinium enhanced sequences showed enhancement in one of the lesions. Thus three out of four of the Barkhof criteria were fulfilled.[30] Images obtained from this subject can be seen in Figure 2. Because of the MRI findings, she was referred to a neurologist in March where a second neurological examination was normal. CSF analysis revealed oligoclonal bands and an elevated IgG index. In May she returned to the neurological clinic due to a sudden onset of intermittent bilateral symptoms in arms and hands. A new neurological examination revealed bilateral tremor and dysmetria. A new MRI in June showed three new non-enhancing supratentorial lesions. She was diagnosed with MS and at a follow-up in September the symptoms in the upper extremities had worsened. She received prednisolone treatment and was started on interferon beta therapy. In November she had Lhermitte's sign and a MRI showed a cervical spine lesion. Except for

one occurrence of lower extremity symptoms in 2005, ~~Since then~~ she has remained relapse free as of the latest neurological follow-up in March 2013~~2010~~.

DISCUSSION

This study shows that RIS, according to present stringent criteria, is an uncommon finding, in a tertiary radiological clinic in a region with a high prevalence of MS, where awareness and clinical suspicion of MS is common.[29] The RIS frequency of 0.05% is in alignment with previous anatomo-pathological studies and earlier MRI studies have shown that "incidental" or "asymptomatic" MS is relatively uncommon.[19–26] The ~~highest~~ only ~~known~~ reported frequency of RIS since its definition, 0·7%, comes from a report from the Karachi region of Pakistan.[27] In contrast, the current study reports a frequency of RIS of 0·15% in the same age group. Although the studies are not directly comparable due to dissimilarities in methodology, it is of interest to consider the difference in results further. A possible explanation may be the high awareness of MS in Sweden and frequent clinical suspicion when referring patients for MRI. The results could possibly also be affected by the fact that a majority of the referrals to the radiological clinic participating in this study comes from the in-hospital clinics, whilst patients initially seeking their family practitioner might have been referred to a non-tertiary radiological clinic for an MRI. How the fact that the study site is a tertiary setting has affected the reported prevalence is therefore hard to appreciate. Another explanation for the difference might be that the study from Pakistan was a semi-retrospective and -prospective study, which might have been more effective in identifying patients with these findings and suffering from less losses to follow-up. In the study from Pakistan there were also fewer patients examined in a more densely populated area, likely mirroring a lower availability of MRI in the Karachi region than the Stockholm region, perhaps making the patients who were examined with a MRI of the brain in Karachi more likely to have findings. The published RIS cohorts are samples from Brazil, France, Italy, Spain, Turkey, and USA,[2,7,11–17] regions that vary from

low to high prevalence.[31] It would be of interest to further evaluate the RIS prevalence in relation to the global MS prevalence.

A limitation of this study is the retrospective design with a single rater that may have led to patients being missed in the screening although a systematic approach was taken. By relying on the clinical evaluations in the screening process it is possible that patients with findings fulfilling the Barkhof criteria were missed. We believe that such gross errors are unlikely since at least one neuroradiologist and in total usually two radiologists evaluated all examinations as part of the clinical diagnostics. This being said, any patient missed would affect the reported frequency significantly due to the low prevalence of RIS. In terms of losses to follow-up, assuming that the frequency of RIS was the same in the 17 plausible RIS patients lost to follow-up as in those with all data available (1 case of RIS in 36 patients with plausible RIS), this would be equivalent to 1/36 x 17 = 0.47. This would increase the RIS frequency to 0.07%, or double the reported frequency to 0.1%, if rounded up to one patient. It is also unexpected that no elderly patients were classified as RIS since the presence of asymptomatic white matter lesions increase with age.[32] This might be due to the clinical information being available in the screening process, making it more likely to classify these white matter changes as ischemic-degenerative. The study period was chosen to be the year 2001 in order to be able to show the natural long-term prognosis for the RIS cases identified. The reasoning for this was that regarding the published RIS cohorts, especially the retrospective cohorts, it is often unclear how the patients were initially identified. The hypothesis was therefore that patients with RIS that do not progress clinically are less likely to be noticed in the clinical setting, decreasing the chance of being included in a cohort, giving the observed cohort a worse prognosis. The study design did unfortunately not prove very helpful since only one case was identified, which limits the possibility of studying the prognosis. Although the study was conducted in 2001, it was conducted on modern 1·5 T

MRI machines why the low frequency of RIS findings is hardly explained by technical reasons.

In conclusion this study suggest that RIS, according to present stringent criteria, is an uncommon finding in a tertiary setting in a region with a high prevalence of MS. In order to more accurately determine the frequency of RIS in relation to MS prevalence, non-selected populations in large prospective studies actively involving both radiologists and neurologists are needed. In order to be able to study the prognosis of these patients large multi-center studies or case-control studies are recommended.

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FOOT NOTES

Contributors

TG initiated the study, designed data collection tools, performed the screening of all MRI examinations, monitored data collection, and drafted the paper. He is guarantor. JM performed neuroradiological image analysis. TG, JM, MKW, PA and SF all conceived and designed the study, analysed the data, and revised the paper.

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Competing interests

SF has received honoraria for lectures or educational activities from Allergan, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. All other authors declare no competing interests.

Ethics approval

This study was conducted with the approval of the regional ethical review board in Stockholm at Karolinska Institutet.

Patient consent

Obtained.

Data sharing statement

No additional data are available.

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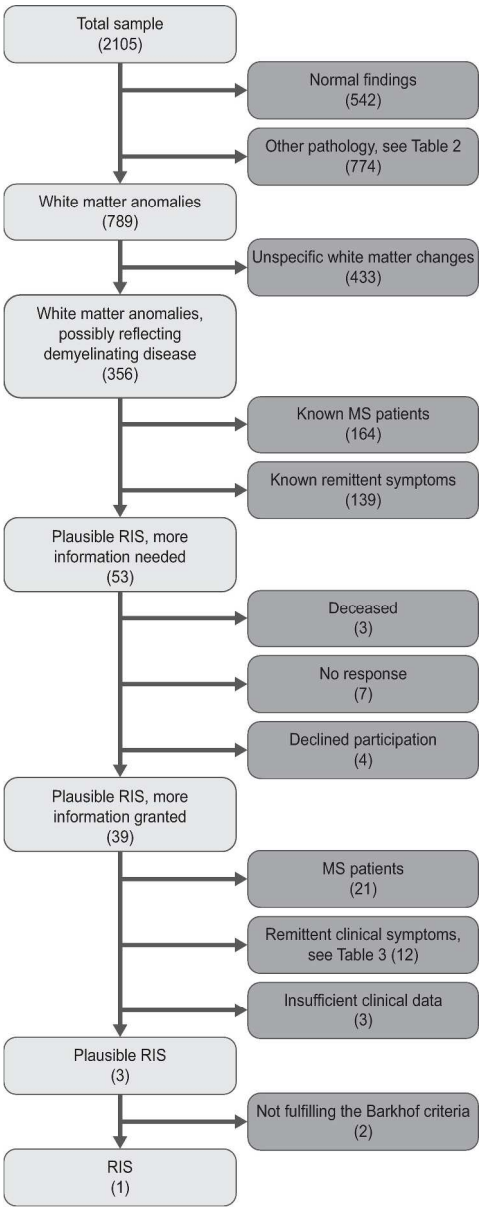
Figure 1

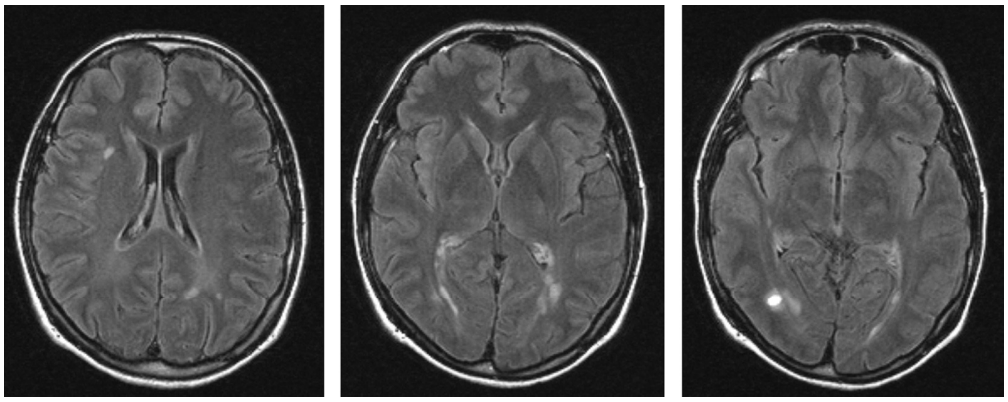
Flow chart of the screening process to identify patients with possible RIS

Figure 2

Axial FLAIR images of the identified RIS patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image



Flow chart of the screening process to identify patients with possible RIS
209x531mm (300 x 300 DPI)



Axial FLAIR images of the identified RIS patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image
173x67mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis

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Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis

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ABSTRACT

Objective: The improved availability of magnetic resonance imaging (MRI) in medicine has led to an increase in incidental findings. Unexpected brain MRI findings suggestive of multiple sclerosis (MS) without typical symptoms of MS were recently defined as radiologically isolated syndrome (RIS). The prevalence of RIS is uncertain. The aim of this study was to determine the prevalence of RIS at a university hospital in a region with a high prevalence for MS and describe the long-term prognosis of the identified patients.

Design: Retrospective cohort study conducted in 2012.

Setting: All brain MRI examinations performed at Karolinska University Hospital in Huddinge, Stockholm, Sweden during 2001 were retrospectively screened by a single rater for findings fulfilling the Okuda criteria. The sample year was chosen in order to establish the long-term prognosis of the patients identified. The examinations of interest were re-evaluated according to the Barkhof criteria by a neuroradiologist with long experience in MS.

Participants: In total 2105 individuals were included in the study. Ages ranged from 0 to 90 years with a median age of 48 years. Only one patient with RIS was identified, equivalent to a prevalence of 0·05% in the studied population, or 0·15% among patients aged 15 to 40 years. The patient with RIS developed symptoms consistent with MS within three months accompanied with radiological progression and was diagnosed with MS.

Conclusions: RIS, according to present criteria, is an uncommon finding in a tertiary hospital setting in a high-prevalence region for MS where awareness and clinical suspicion of MS is common. In order to study the prognosis of RIS, multi-center studies, or case-control studies are recommended.

ARTICLE SUMMARY

Article focus

- Incidental magnetic resonance imaging findings suggestive of multiple sclerosis in patients without typical symptoms of demyelinating disease is called Radiologically Isolated Syndrome and poses a clinical dilemma for physicians.
- The aim of this study was to investigate the prevalence of the newly defined Radiologically Isolated Syndrome at a university clinic in Stockholm, Sweden.

Key messages

- Radiologically Isolated Syndrome was an uncommon finding, and was identified only in 1 out of 2105 examined individuals (0.05 %).
- The patient rapidly progressed radiologically and clinically to multiple sclerosis.

Strengths and limitations of this study

- This is the first study reporting on the frequency of Radiologically Isolated Syndrome in a high-prevalence region for multiple sclerosis.
- The study was a systematic re-evaluation of a yearly sample at a large university clinic.
- The retrospective nature of the study gives the possibility to report on the long-term prognosis for the patients, but also gives rise to losses to follow-up.
- The generalizability of the results to non-tertiary hospital settings and to regions with a

lower prevalence of multiple sclerosis is limited.

INTRODUCTION

Magnetic resonance imaging (MRI) has revolutionised our ability to image the central nervous system and it has become readily accessible in clinical practice. With the improved availability and sensitivity of MRI there is an increase in incidental findings.[1] In 2009, Okuda and colleagues defined incidental MRI findings suggestive of multiple sclerosis (MS) without typical MS symptoms as Radiologically Isolated Syndrome (RIS).[2] This has led to an increased awareness of this condition and a convergence in terminology.[3]

Since the definition of RIS, studies by several groups have shown that there is a close association between RIS and MS. Patients with RIS often have a subclinical cognitive impairment with a similar test profile of deficits compared to patients with MS.[4–6] The association of RIS and MS is also strengthened in that both patient groups show similarities in both qualitative and quantitative MRI measurements.[6–8] There are case reports with follow-ups of up to 10 years,[4,9,10] and the range of mean follow-up times in the published cohorts are 2·4 to 7 years.[2,11–17] These studies show that roughly two-thirds progress radiologically and one-third develop clinical symptoms, and thereby convert to clinically isolated syndrome or MS, during their follow-up times.[3] This suggests that RIS in some cases may be considered to be preclinical MS. The patients with RIS is therefore of particular interest to study in a pathophysiological aspect since it may shed light on early changes that precedes the onset of classical MS symptoms.

Headache is the most common reason for performing the initial MRI unveiling RIS, but it is unclear if there is a causative relationship between the incidental MRI findings and the headaches.[3] Recently a study by Liu and colleagues showed that among patients undergoing a MRI of the brain due to headaches, MRI findings fulfilling the Barkhof criteria are common.

Depending on the definition of juxtacortical and periventricular, 2·4–7·1% of the patients fulfilled the Barkhof criteria.[18]

Incidental MS findings are previously known from autopsy studies from the late 20th century indicating a frequency of unexpected post-mortem MS findings in the range of 0·08–0·2%.[19–22] The incidence and prevalence of the newly defined RIS is, however, currently unknown.[3] In 2009 Morris and colleagues published a meta-analysis of 16 studies including 15,559 healthy control subjects that reported nine cases of "definite demyelination" and four cases of "possible demyelination" corresponding to a frequency of 0·06% and 0·03% respectively.[1] There is unfortunately no report on the clinical history or neurological examination of these cases why the results cannot be assumed to reflect RIS. Instead the results of five original articles, identified as the most relevant, are described below.

An American study published in 1996, described 23 patients with MRI findings highly suggestive of MS (according to Paty's classification) in a population of 2,783 psychiatric patients. However, 13 patients had neurological symptoms that were not further specified, which gives a possible asymptomatic frequency of roughly 0·4%. It is unknown if these patients had any neurological findings that would exclude them from a RIS diagnosis.[23] The results are nonetheless interesting since psychiatric symptoms have frequently been reported as the original indication for performing the MRI examination that unveiled the RIS.[3] A second American study published in 1999 showed that among 1,000 asymptomatic subjects, there where three persons (0·3%) with findings classified as possible demyelinating disease.[24] A German study published in 2006 described a cohort of 2,536 young male military recruits in which one person (0·04%) had findings suggestive of demyelinating disease, but it is not specified if this person had any neurological symptoms or findings.[25] A second German study was published in 2010, which showed that of 206 healthy young volunteers two (1·0%) had

multiple white matter lesions, but it is unclear whether the findings fulfilled the Barkhof criteria.[26]

The first study reporting on the frequency of RIS since its definition was a hospital-based study from Pakistan published in 2011. It revealed that out of 864 persons in the ages 15 to 40 years there were six cases (0·7%) of incidental MRI findings suggestive of MS in patients without relapsing neurological symptoms or pathological neurological findings.[27] This study reported a surprisingly high frequency of such findings in a region with a low prevalence of MS (<5 per 100,000 population).[28] In comparison the estimated prevalence of MS in Sweden, where the present study was conducted, is 189 per 100,000 population.[29] Recently a second study using the RIS criteria was published in 2013 that demonstrated the frequency of RIS findings in asymptomatic relatives to MS patients and healthy controls. It showed that 2 out of 68 (2·9%) healthy relatives of MS patients and that 2 out of 82 (2·4%) of the healthy controls fulfilled the Okuda criteria.[30]

In conclusion there has not been any study reporting on the hospital-based prevalence of RIS in a high-prevalence region for MS since the definition of RIS. This study aims to clarify in what frequency RIS findings can be expected in a tertiary hospital setting in a high-prevalence region for MS and depict the long-term prognosis of RIS in the patients identified.

METHODS

Study population and ethical approval

The study sample in this retrospective study conducted in 2012 is based on the digital radiological information system and digital patient charts at Karolinska University Hospital, Huddinge (formerly Huddinge University Hospital), Stockholm, Sweden. The hospital is a tertiary referral hospital for the greater southern Stockholm area with a population of 800,000

inhabitants. Although the study was conducted in 2012, the sample year was chosen to be 2001, when both the patient charts and the radiological data were fully digitalised, in order to be able to show the natural long-term prognosis over the past 11 years for any RIS cases identified. All persons undergoing a brain MRI at the hospital during the sample year were included in the study. The study was approved by the regional ethical review board in Stockholm at Karolinska Institutet, which allowed a general screening of the examinations described above, and written informed consent was obtained according to the approval in those cases where more information was necessary through access of the clinical patient charts.

Screening method

The screening of the study population was made systematically by one physician at the radiology department with previous experience of radiological research (TG). All documentation from the MRI examinations from 2001 was available to the screener and read to full extent. The material included both the query, the clinical information in the referral (clinical history, symptoms, and findings) as well as the radiological findings according to the regular clinical radiological assessment.

MRI examinations

All MRI examinations were performed in the regular clinical setting in one of two 1·5 T MRI machines, Siemens Magnetom Vision and Symphony (Siemens Medical Systems GmbH, Erlangen, Germany). The MRI examinations were performed according to standard clinical protocols depending on the original clinical query and white matter anomalies were in most cases further characterised with the standardised MS MRI protocol used at the clinic described in Table 1.

Table 1

MRI parameters of the standardised MS protocol

Sequence	Plane	SLT (mm)	TR (ms)	TE (ms)	TI (ms)	FA (°)
T1 MPRAGE	Axial	1·5	13·5	7	300	15
PD TSE	Axial	3·0	4761	22	-	180
T2 TSE	Axial	3·0	4761	90	-	180
T2 TSE*	Sagittal	4·0	3500	96	-	180
FLAIR*	Axial	5·0	9000	110	2500	180
T1 SE*	Axial	5·0	570	14	-	90

*Acquired post-gadolinium-DTPA contrast media.
FA, flip angle; FLAIR, fluid attenuated inversion recovery; MPRAGE, three-dimensional magnetization prepared rapid acquisition gradient echo; PD, proton density; SE, spin echo; SLT, slice thickness; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo.

Radiological assessment

All examinations had been reviewed, signed, and contra-signed as part of the regular clinical radiological routine. At least one of the clinical reviewers was a specialist in neuroradiology. The examinations identified with possible RIS findings in the screening process were re-evaluated according to the Barkhof criteria by another neuroradiologist (JM) with long experience of classifying MS-like findings.

Clinical assessment

The referring doctor conducted the initial clinical assessments. All patients that were identified as possible RIS cases in the screening had been examined by a neurologists as part of the following clinical investigation. All patients diagnosed with MS received their diagnosis according to contemporaneous diagnostic criteria after careful investigation lead by a neurologist with experience of MS.

RESULTS

Prevalence of RIS

During the year of 2001 a total of 2105 individuals had at least one MRI examination of the brain at Karolinska University Hospital in Huddinge, Stockholm, Sweden. Among the

patients there were 903 men (43%) and 1202 women (57%) with an age span of 0 to 90 years with 669 persons being between 15 and 40 years of age. Mean age was 46·2 years and median age was 48 years. The following results are also schematically described in Figure 1. Out of all patients 542 had normal findings. The spectrum of findings is presented in Table 2. Common findings besides white matter changes were tumours, atrophy, infarctions, and sinusitis.

Table 2

Overview of MRI findings (n)

Within normal limits	**542**
Cerebrovascular disorders	**326**
- Aneurysm	8
- Carotid dissection or occlusion	12
- Cavernous malformation	19
- Cerebral contusions	4
- Cortical infarction	89
- Developmental venous anomaly	29
- Lacunar infarction	133
- Intracerebral haemorrhage	15
- Cerebral venous sinus thrombosis	5
- Subarachnoid haemorrhage	3
- Subdural hematoma or hygroma	6
- Other	3
White matter and neurodegenerative disorders	**1143**
- Atrophy	285
- Basal ganglia disorders	12
- Hydrocefalus	20
- Marked perivascular spaces	37
- Possibly inflammatory white matter changes	356
- Unspecific or degenerative white matter changes	433
Infectious, inflammatory and metabolic disorders	**88**
- Cerebral abscess	7
- Congenital metabolic disorders	4

- Encephalitis	10
- Meningitis	15
- Optical neuritis	37
- Vasculitis	4
- Other	11
Neoplasms	**311**
- Acoustic neuroma	19
- Glioma	21
- Meningioma	44
- Metastasis	18
- Pituitary adenoma	31
- Unspecified or other type of neoplasm	46
Cysts and malformations	**74**
- Arachnoid cyst	24
- Empty sella	9
- Malformation or dysplasia	16
- Parenchymal cyst	5
- Pineal cyst	13
- Pituitary cyst	7
Sinonasal and orbital disorders	**191**
- Sinusitis	164
- Mastoiditis	23
- Other	4

In total 789 patients had white matter anomalies (not involving those caused by other diseases). Out of these patients, 433 had unspecific white matter changes that did not fulfil the Barkhof criteria (solitary findings) or had a more likely explanation; such as an ischemic-degenerative pattern in elderly and/or patients with known severe cardiovascular disease. Out of the 356 patients with white matter changes possibly reflecting demyelinating disease, 158 patients were known to have MS and 6 received their MS diagnosis as part of the investigation in question. Out of the 192 remaining patients 139 were reported to have apparent neurological symptoms in the referral that would exclude the findings from being classified as RIS according to the B criteria in the Okuda classification, but where it was

unclear if they had already gotten a diagnosis of Clinically Isolated Syndrome or MS. After this screening only 53 patients remained with findings that were plausible RIS but where more clinical information was needed. In compliance with the ethical approval these patients were asked for written informed consent in order for us to evaluate their clinical patient charts.

Of these 53 patients where further information was needed, 3 patients were deceased, 7 did not respond and 4 declined participation. The patient charts of the remaining 39 persons that gave their informed consent were then examined in order to better understand the patients' clinical history, symptoms and neurological findings. This additional information revealed that 21 had been diagnosed with MS. Another 12 had intermittent clinical symptoms dismissing a RIS classification, presented in Table 3, but where the patients had not yet received a diagnosis of MS. In 3 cases there was insufficient clinical data to draw a conclusion. In the end, 3 patients with plausible RIS remained and after neuroradiological assessment 1 patient was classified as having RIS. This is equivalent to a prevalence of 0·05% in the studied population and 0·15% among the patients in the ages of 15 to 40 years.

Table 3

Presenting symptoms in the 12 patients not classified as RIS

Sex	Age (years)	Symptoms
F	25	Optical neuritis, Lhermitte's sign
F	26	Diplopia, hemiparesis
F	39	Optical neuritis, facial hemidysesthesia
F	43	Optical neuritis
F	47	Recurrent hemidysesthesia
F	58	Trigeminal neuralgia
F	62	Hemidysesthesia, facial paralysis
F	62	Hemidysesthesia
M	18	Severe vertigo, ataxia
M	18	Lhermitte's sign
M	27	Diplopia, vertigo, dysesthesia
M	44	Hypesthesia

F, female; M, male.

Case description

The patient with RIS was a 43 year-old woman without any neurological symptoms or any history of neurological disorders except for migraine since more than 10 years. A neurological examination did not reveal any pathological findings. She had good effect of triptanes. Due to her long history of migraine and still frequent attacks she was referred for a MRI of the brain in February of 2001. The scan showed 15 supratentorial T2 lesions, out of which 12 were periventricular and 2 were juxtacortical. Gadolinium enhanced sequences showed enhancement in one of the lesions. Thus three out of four of the Barkhof criteria were fulfilled.[31] Images obtained from this subject can be seen in Figure 2. Because of the MRI findings, she was referred to a neurologist in March where a second neurological examination was normal. CSF analysis revealed oligoclonal bands and an elevated IgG index. In May she returned to the neurological clinic due to a sudden onset of intermittent bilateral symptoms in arms and hands. A new neurological examination revealed bilateral tremor and dysmetria. A new MRI in June showed three new non-enhancing supratentorial lesions. She was diagnosed with MS and at a follow-up in September the symptoms in the upper extremities had worsened. She received prednisolone treatment and was started on interferon beta therapy. In November she had Lhermitte's sign and a MRI showed a cervical spine lesion. Except for one occurrence of lower extremity symptoms in 2005, she has remained relapse free as of the latest neurological follow-up in March 2013.

DISCUSSION

This study shows that RIS, according to present stringent criteria, is an uncommon finding, in a tertiary radiological clinic in a region with a high prevalence of MS, where awareness and clinical suspicion of MS is common.[29] The RIS frequency of 0.05% is in alignment with previous anatomo-pathological studies and earlier MRI studies have shown that "incidental"

or "asymptomatic" MS is relatively uncommon.[19–26] The only hospital-based reported frequency of RIS since its definition, 0·7%, comes from a report from the Karachi region of Pakistan.[27] In contrast, the current study reports a frequency of RIS of 0·15% in the same age group. Although the studies are not directly comparable due to dissimilarities in methodology, it is of interest to consider the difference in results further. A possible explanation may be the high awareness of MS in Sweden and frequent clinical suspicion when referring patients for MRI. The results could possibly also be affected by the fact that a majority of the referrals to the radiological clinic participating in this study comes from the in-hospital clinics, whilst patients initially seeking their family practitioner might have been referred to a non-tertiary radiological clinic for an MRI. How the fact that the study site is a tertiary setting has affected the reported prevalence is therefore hard to appreciate. Another explanation for the difference might be that the study from Pakistan was a semi-retrospective and -prospective study, which might have been more effective in identifying patients with these findings and suffering from less losses to follow-up. In the study from Pakistan there were also fewer patients examined in a more densely populated area, likely mirroring a lower availability of MRI in the Karachi region than the Stockholm region, perhaps making the patients who were examined with a MRI of the brain in Karachi more likely to have findings. The published RIS cohorts are samples from Brazil, France, Italy, Spain, Turkey, and USA,[2,7,11–17] regions that vary from low to high prevalence.[32] It would be of interest to further evaluate the RIS prevalence in relation to the global MS prevalence.

Interestingly, the study published by Gabelic and colleagues shows that 2·9% of the healthy relatives of MS patients and 2·4% of the healthy controls in their study fulfilled Okuda's RIS criteria.[30] This might indicate that the frequency of RIS findings would paradoxically be higher in the general population than found in the current study. However, differences in methodologies and demography of the research subjects limit the comparability of the current

study to Gabelic's work. The studies were not performed in the same region and with different aims. While this study aimed to describe the hospital-based frequency of RIS without limitations in terms of age groups, Gabelic's study was performed in a different country and studied the frequency of RIS in healthy hospital personnel and volunteers recruited through newspaper advertisement within a homogenous age group with a mean age of 40 years.

A limitation of this study is the retrospective design with a single rater that may have led to patients being missed in the screening although a systematic approach was taken. By relying on the clinical evaluations in the screening process it is possible that patients with findings fulfilling the Barkhof criteria were missed. We believe that such gross errors are unlikely since at least one neuroradiologist and in total usually two radiologists evaluated all examinations as part of the clinical diagnostics. This being said, any patient missed would affect the reported frequency significantly due to the low prevalence of RIS. In terms of losses to follow-up, assuming that the frequency of RIS was the same in the 17 plausible RIS patients lost to follow-up as in those with all data available (1 case of RIS in 36 patients with plausible RIS), this would be equivalent to 1/36 x 17 = 0.47. This would increase the RIS frequency to 0.07%, or double the reported frequency to 0.1%, if rounded up to one patient. It is also unexpected that no elderly patients were classified as RIS since the presence of asymptomatic white matter lesions increase with age.[33] This might be due to the clinical information being available in the screening process, making it more likely to classify these white matter changes as ischemic-degenerative. The study period was chosen to be the year 2001 in order to be able to show the natural long-term prognosis for the RIS cases identified with a potential follow-up period of 11 years. The reasoning for this was that regarding the published RIS cohorts, especially the retrospective cohorts, it is often unclear how the patients were initially identified. The hypothesis was therefore that patients with RIS that do not

progress clinically are less likely to be noticed in the clinical setting, decreasing the chance of being included in a cohort, giving the observed cohort a worse prognosis. The study design did unfortunately not prove very helpful since only one case was identified, which limits the possibility of studying the prognosis. Although the study was conducted in 2001, it was conducted on modern 1·5 T MRI machines why the low frequency of RIS findings is hardly explained by technical reasons.

In conclusion this study suggest that RIS, according to present stringent criteria, is an uncommon finding in a tertiary hospital setting in a region with a high prevalence of MS. In order to more accurately determine the frequency of RIS in relation to MS prevalence, non-selected populations in large prospective studies actively involving both radiologists and neurologists are needed. In order to be able to study the prognosis of these patients large multi-center studies or case-control studies are recommended.

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FOOT NOTES

Contributors

TG initiated the study, designed data collection tools, performed the screening of all MRI examinations, monitored data collection, and drafted the paper. He is guarantor. JM performed neuroradiological image analysis. TG, JM, MKW, PA and SF all conceived and designed the study, analysed the data, and revised the paper.

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Competing interests

SF has received honoraria for lectures or educational activities from Allergan, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. All other authors declare no competing interests.

Ethics approval

This study was conducted with the approval of the regional ethical review board in Stockholm at Karolinska Institutet.

Patient consent

Obtained.

Data sharing statement

No additional data are available.

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Figure 1

Flow chart of the screening process to identify patients with possible RIS

Figure 2

Axial FLAIR images of the identified RIS patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image

Radiologically isolated syndrome - an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis

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ABSTRACT

Objective: The improved availability of magnetic resonance imaging (MRI) in medicine has led to an increase in incidental findings. Unexpected brain MRI findings suggestive of multiple sclerosis (MS) without typical symptoms of MS were recently defined as radiologically isolated syndrome (RIS). The prevalence of RIS is uncertain. The aim of this study was to determine the prevalence of RIS at a university hospital in a region with a high prevalence for MS and describe the long-term prognosis of the identified patients.

Design: Retrospective cohort study conducted in 2012.

Setting: All brain MRI examinations performed at Karolinska University Hospital in Huddinge, Stockholm, Sweden during 2001 were retrospectively screened by a single rater for findings fulfilling the Okuda criteria. The sample year was chosen in order to establish the long-term prognosis of the patients identified. The examinations of interest were re-evaluated according to the Barkhof criteria by a neuroradiologist with long experience in MS.

Participants: In total 2105 individuals were included in the study. Ages ranged from 0 to 90 years with a median age of 48 years. Only one patient with RIS was identified, equivalent to a prevalence of 0·05% in the studied population, or 0·15% among patients aged 15 to 40 years. The patient with RIS developed symptoms consistent with MS within three months accompanied with radiological progression and was diagnosed with MS.

Conclusions: RIS, according to present criteria, is an uncommon finding in a tertiary hospital setting in a high-prevalence region for MS where awareness and clinical suspicion of MS is common. In order to study the prognosis of RIS, multi-center studies, or case-control studies are recommended.

ARTICLE SUMMARY

Article focus

- Incidental magnetic resonance imaging findings suggestive of multiple sclerosis in patients without typical symptoms of demyelinating disease is called Radiologically Isolated Syndrome and poses a clinical dilemma for physicians.
- The aim of this study was to investigate the prevalence of the newly defined Radiologically Isolated Syndrome at a university clinic in Stockholm, Sweden.

Key messages

- Radiologically Isolated Syndrome was an uncommon finding, and was identified only in 1 out of 2105 examined individuals (0.05 %).
- The patient rapidly progressed radiologically and clinically to multiple sclerosis.

Strengths and limitations of this study

- This is the first study reporting on the frequency of Radiologically Isolated Syndrome in a high-prevalence region for multiple sclerosis.
- The study was a systematic re-evaluation of a yearly sample at a large university clinic.
- The retrospective nature of the study gives the possibility to report on the long-term prognosis for the patients, but also gives rise to losses to follow-up.
- The generalizability of the results to non-tertiary hospital settings and to regions with a

lower prevalence of multiple sclerosis is limited.

INTRODUCTION

Magnetic resonance imaging (MRI) has revolutionised our ability to image the central nervous system and it has become readily accessible in clinical practice. With the improved availability and sensitivity of MRI there is an increase in incidental findings.[1] In 2009, Okuda and colleagues defined incidental MRI findings suggestive of multiple sclerosis (MS) without typical MS symptoms as Radiologically Isolated Syndrome (RIS).[2] This has led to an increased awareness of this condition and a convergence in terminology.[3]

Since the definition of RIS, studies by ~~Lebrun, Okuda, de Stefano, Amato, Siva, Giorgio, and their colleagues have been especially important in showing~~several groups have shown that there is a close association between RIS and MS. Patients with RIS often have a subclinical cognitive impairment with a similar test profile of deficits compared to patients with MS.[4–6] The association of RIS and MS is also strengthened in that both patient groups show similarities in both qualitative and quantitative MRI measurements.[6–8] There are case reports with follow-ups of up to 10 years,[4,9,10] and the range of mean follow-up times in the published cohorts are 2·4 to 7 years.[2,11–17] These studies show that roughly two-thirds progress radiologically and one-third develop clinical symptoms, and thereby convert to clinically isolated syndrome or MS, during their follow-up times.[3] This suggests that RIS in some cases may be considered to be preclinical MS. The patients with RIS is therefore of particular interest to study in a pathophysiological aspect since it may shed light on early changes that precedes the onset of classical MS symptoms.

Headache is the most common reason for performing the initial MRI unveiling RIS, but it is unclear if there is a causative relationship between the incidental MRI findings and the headaches.[3] Recently a study by Liu and colleagues showed that among patients undergoing a MRI of the brain due to headaches, MRI findings fulfilling the Barkhof criteria are common.

Depending on the definition of juxtacortical and periventricular, 2·4–7·1% of the patients fulfilled the Barkhof criteria.[18]

Incidental MS findings are previously known from autopsy studies from the late 20th century indicating a frequency of unexpected post-mortem MS findings in the range of 0·08–0·2%.[19–22] The incidence and prevalence of the newly defined RIS is, however, currently unknown.[3] In 2009 Morris and colleagues published a meta-analysis of 16 studies including 15,559 healthy control subjects that reported nine cases of "definite demyelination" and four cases of "possible demyelination" corresponding to a frequency of 0·06% and 0·03% respectively.[1] There is unfortunately no report on the clinical history or neurological examination of these cases why the results cannot be assumed to reflect RIS. Instead the results of five original articles, identified as the most relevant, are described below.

An American study published in 1996, described 23 patients with MRI findings highly suggestive of MS (according to Paty's classification) in a population of 2,783 psychiatric patients. However, 13 patients had neurological symptoms that were not further specified, which gives a possible asymptomatic frequency of roughly 0·4%. It is unknown if these patients had any neurological findings that would exclude them from a RIS diagnosis.[23] The results are nonetheless interesting since psychiatric symptoms have frequently been reported as the original indication for performing the MRI examination that unveiled the RIS.[3] A second American study published in 1999 showed that among 1,000 asymptomatic subjects, there where three persons (0·3%) with findings classified as possible demyelinating disease.[24] A German study published in 2006 described a cohort of 2,536 young male military recruits in which one person (0·04%) had findings suggestive of demyelinating disease, but it is not specified if this person had any neurological symptoms or findings.[25] A second German study was published in 2010, which showed that of 206 healthy young volunteers two (1·0%) had

multiple white matter lesions, but it is unclear whether the findings fulfilled the Barkhof criteria.[26]

The ~~only~~ first study reporting on the frequency of RIS since its definition ~~comes~~ was a hospital-based study from Pakistan published in 2011. It revealed that out of 864 persons in the ages 15 to 40 years there were six cases (0·7%) of incidental MRI findings suggestive of MS in patients without relapsing neurological symptoms or pathological neurological findings.[27] This ~~last~~ study reported a surprisingly high frequency of such findings in a region with a low prevalence of MS (<5 per 100,000 population).[28] In comparison the estimated prevalence of MS in Sweden, where the present study was conducted, is 189 per 100,000 population.[29] Recently a second study using the RIS criteria was published in 2013 that demonstrated the frequency of RIS findings in asymptomatic relatives to MS patients and healthy controls. It showed that 2 out of 68 (2·9%) healthy relatives of MS patients and that 2 out of 82 (2·4%) of the healthy controls fulfilled the Okuda criteria.[30]

In conclusion there has not been any study reporting on the hospital-based prevalence of RIS in a high-prevalence region for MS since the definition of RIS. This study aims to clarify in what frequency RIS findings can be expected in a tertiary hospital setting in a high-prevalence region for MS and depict the long-term prognosis of RIS in the patients identified.

METHODS

Study population and ethical approval

The study sample in this retrospective study conducted in 2012 is based on the digital radiological information system and digital patient charts at Karolinska University Hospital, Huddinge (formerly Huddinge University Hospital), Stockholm, Sweden. The hospital is a tertiary referral hospital for the greater southern Stockholm area with a population of 800,000

inhabitants. Although the study was conducted in 2012, the sample year was chosen to be 2001~~In order to establish the long-term prognosis of the patients identified the sample year was chosen to 2001~~, when both the patient charts and the radiological data were fully digitalised, in order to be able to show the natural long-term prognosis over the past 11 years for any RIS cases identified. All persons undergoing a brain MRI at the hospital during the sample year were included in the study. The study was approved by the regional ethical review board in Stockholm at Karolinska Institutet, which allowed a general screening of the examinations described above, and written informed consent was obtained according to the approval in those cases where more information was necessary through access of the clinical patient charts.

Screening method

The screening of the study population was made systematically by one physician at the radiology department with previous experience of radiological research (TG). All documentation from the MRI examinations from 2001 was available to the screener and read to full extent. The material included both the query, the clinical information in the referral (clinical history, symptoms, and findings) as well as the radiological findings according to the regular clinical radiological assessment.

MRI examinations

All MRI examinations were performed in the regular clinical setting in one of two 1·5 T MRI machines, Siemens Magnetom Vision and Symphony (Siemens Medical Systems GmbH, Erlangen, Germany). The MRI examinations were performed according to standard clinical protocols depending on the original clinical query and white matter anomalies were in most cases further characterised with the standardised MS MRI protocol used at the clinic described in Table 1.

Table 1

MRI parameters of the standardised MS protocol

Sequence	Plane	SLT (mm)	TR (ms)	TE (ms)	TI (ms)	FA (°)
T1 MPRAGE	Axial	1·5	13·5	7	300	15
PD TSE	Axial	3·0	4761	22	-	180
T2 TSE	Axial	3·0	4761	90	-	180
T2 TSE*	Sagittal	4·0	3500	96	-	180
FLAIR*	Axial	5·0	9000	110	2500	180
T1 SE*	Axial	5·0	570	14	-	90

*Acquired post-gadolinium-DTPA contrast media.
FA, flip angle; FLAIR, fluid attenuated inversion recovery; MPRAGE, three-dimensional magnetization prepared rapid acquisition gradient echo; PD, proton density; SE, spin echo; SLT, slice thickness; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo.

Radiological assessment

All examinations had been reviewed, signed, and contra-signed as part of the regular clinical radiological routine. At least one of the clinical reviewers was a specialist in neuroradiology. The examinations identified with possible RIS findings in the screening process were re-evaluated according to the Barkhof criteria by another neuroradiologist (JM) with long experience of classifying MS-like findings.

Clinical assessment

The referring doctor conducted the initial clinical assessments. All patients that were identified as possible RIS cases in the screening had been examined by a neurologists as part of the following clinical investigation. All patients diagnosed with MS received their diagnosis according to contemporaneous diagnostic criteria after careful investigation lead by a neurologist with experience of MS.

RESULTS

Prevalence of RIS

During the year of 2001 a total of 2105 individuals had at least one MRI examination of the brain at Karolinska University Hospital in Huddinge, Stockholm, Sweden. Among the patients there were 903 men (43%) and 1202 women (57%) with an age span of 0 to 90 years with 669 persons being between 15 and 40 years of age. Mean age was 46·2 years and median age was 48 years. The following results are also schematically described in Figure 1. Out of all patients 542 had normal findings. The spectrum of findings is presented in Table 2. Common findings besides white matter changes were tumours, atrophy, infarctions, and sinusitis.

Table 2

Overview of MRI findings (n)

Within normal limits	**542**
Cerebrovascular disorders	**326**
- Aneurysm	8
- Carotid dissection or occlusion	12
- Cavernous malformation	19
- Cerebral contusions	4
- Cortical infarction	89
- Developmental venous anomaly	29
- Lacunar infarction	133
- Intracerebral haemorrhage	15
- Cerebral venous sinus thrombosis	5
- Subarachnoid haemorrhage	3
- Subdural hematoma or hygroma	6
- Other	3
White matter and neurodegenerative disorders	**1143**
- Atrophy	285
- Basal ganglia disorders	12
- Hydrocefalus	20
- Marked perivascular spaces	37
- Possibly inflammatory white matter changes	356
- Unspecific or degenerative white matter changes	433

Infectious, inflammatory and metabolic disorders	**88**
- Cerebral abscess	7
- Congenital metabolic disorders	4
- Encephalitis	10
- Meningitis	15
- Optical neuritis	37
- Vasculitis	4
- Other	11
Neoplasms	**311**
- Acoustic neuroma	19
- Glioma	21
- Meningioma	44
- Metastasis	18
- Pituitary adenoma	31
- Unspecified or other type of neoplasm	46
Cysts and malformations	**74**
- Arachnoid cyst	24
- Empty sella	9
- Malformation or dysplasia	16
- Parenchymal cyst	5
- Pineal cyst	13
- Pituitary cyst	7
Sinonasal and orbital disorders	**191**
- Sinusitis	164
- Mastoiditis	23
- Other	4

In total 789 patients had white matter anomalies (not involving those caused by other diseases). Out of these patients, 433 had unspecific white matter changes that did not fulfil the Barkhof criteria (solitary findings) or had a more likely explanation; such as an ischemic-degenerative pattern in elderly and/or patients with known severe cardiovascular disease. Out of the 356 patients with white matter changes possibly reflecting demyelinating disease, 158 patients were known to have MS and 6 received their MS diagnosis as part of the investigation in question. Out of the 192 remaining patients 139 were reported to have

apparent neurological symptoms in the referral that would exclude the findings from being classified as RIS according to the B criteria in the Okuda classification, but where it was unclear if they had already gotten a diagnosis of Clinically Isolated Syndrome or MS. After this screening only 53 patients remained with findings that were plausible RIS but where more clinical information was needed. In compliance with the ethical approval these patients were asked for written informed consent in order for us to evaluate their clinical patient charts.

Of these 53 patients where further information was needed, 3 patients were deceased, 7 did not respond and 4 declined participation. The patient charts of the remaining 39 persons that gave their informed consent were then examined in order to better understand the patients' clinical history, symptoms and neurological findings. This additional information revealed that 21 had been diagnosed with MS. Another 12 had intermittent clinical symptoms dismissing a RIS classification, presented in Table 3, but where the patients had not yet received a diagnosis of MS. In 3 cases there was insufficient clinical data to draw a conclusion. In the end, 3 patients with plausible RIS remained and after neuroradiological assessment 1 patient was classified as having RIS. This is equivalent to a prevalence of 0·05% in the studied population and 0·15% among the patients in the ages of 15 to 40 years.

Table 3

Presenting symptoms in the 12 patients not classified as RIS

Sex	Age (years)	Symptoms
F	25	Optical neuritis, Lhermitte's sign
F	26	Diplopia, hemiparesis
F	39	Optical neuritis, facial hemidysesthesia
F	43	Optical neuritis
F	47	Recurrent hemidysesthesia
F	58	Trigeminal neuralgia
F	62	Hemidysesthesia, facial paralysis
F	62	Hemidysesthesia

M	18	Severe vertigo, ataxia
M	18	Lhermitte's sign
M	27	Diplopia, vertigo, dysesthesia
M	44	Hypesthesia

F, female; M, male.

Case description

The patient with RIS was a 43 year-old woman without any neurological symptoms or any history of neurological disorders except for migraine since more than 10 years. A neurological examination did not reveal any pathological findings. She had good effect of triptanes. Due to her long history of migraine and still frequent attacks she was referred for a MRI of the brain in February of 2001. The scan showed 15 supratentorial T2 lesions, out of which 12 were periventricular and 2 were juxtacortical. Gadolinium enhanced sequences showed enhancement in one of the lesions. Thus three out of four of the Barkhof criteria were fulfilled.[31] Images obtained from this subject can be seen in Figure 2. Because of the MRI findings, she was referred to a neurologist in March where a second neurological examination was normal. CSF analysis revealed oligoclonal bands and an elevated IgG index. In May she returned to the neurological clinic due to a sudden onset of intermittent bilateral symptoms in arms and hands. A new neurological examination revealed bilateral tremor and dysmetria. A new MRI in June showed three new non-enhancing supratentorial lesions. She was diagnosed with MS and at a follow-up in September the symptoms in the upper extremities had worsened. She received prednisolone treatment and was started on interferon beta therapy. In November she had Lhermitte's sign and a MRI showed a cervical spine lesion. Except for one occurrence of lower extremity symptoms in 2005, she has remained relapse free as of the latest neurological follow-up in March 2013.

DISCUSSION

This study shows that RIS, according to present stringent criteria, is an uncommon finding, in a tertiary radiological clinic in a region with a high prevalence of MS, where awareness and clinical suspicion of MS is common.[29] The RIS frequency of 0.05% is in alignment with previous anatomo-pathological studies and earlier MRI studies have shown that "incidental" or "asymptomatic" MS is relatively uncommon.[19–26] The only hospital-based reported frequency of RIS since its definition, 0·7%, comes from a report from the Karachi region of Pakistan.[27] In contrast, the current study reports a frequency of RIS of 0·15% in the same age group. Although the studies are not directly comparable due to dissimilarities in methodology, it is of interest to consider the difference in results further. A possible explanation may be the high awareness of MS in Sweden and frequent clinical suspicion when referring patients for MRI. The results could possibly also be affected by the fact that a majority of the referrals to the radiological clinic participating in this study comes from the in-hospital clinics, whilst patients initially seeking their family practitioner might have been referred to a non-tertiary radiological clinic for an MRI. How the fact that the study site is a tertiary setting has affected the reported prevalence is therefore hard to appreciate. Another explanation for the difference might be that the study from Pakistan was a semi-retrospective and -prospective study, which might have been more effective in identifying patients with these findings and suffering from less losses to follow-up. In the study from Pakistan there were also fewer patients examined in a more densely populated area, likely mirroring a lower availability of MRI in the Karachi region than the Stockholm region, perhaps making the patients who were examined with a MRI of the brain in Karachi more likely to have findings. The published RIS cohorts are samples from Brazil, France, Italy, Spain, Turkey, and USA,[2,7,11–17] regions that vary from low to high prevalence.[32] It would be of interest to further evaluate the RIS prevalence in relation to the global MS prevalence.

Interestingly, the study published by Gabelic and colleagues shows that 2·9% of the healthy relatives of MS patients and 2·4% of the healthy controls in their study fulfilled Okuda's RIS criteria.[30] This might indicate that the frequency of RIS findings would paradoxically be higher in the general population than found in the current study. However, differences in methodologies and demography of the research subjects limit the comparability of the current study to Gabelic's work. The studies were not performed in the same region and with different aims. While this study aimed to describe the hospital-based frequency of RIS without limitations in terms of age groups, Gabelic's study was performed in a different country and studied the frequency of RIS in healthy hospital personnel and volunteers recruited through newspaper advertisement within a homogenous age group with a mean age of 40 years.

A limitation of this study is the retrospective design with a single rater that may have led to patients being missed in the screening although a systematic approach was taken. By relying on the clinical evaluations in the screening process it is possible that patients with findings fulfilling the Barkhof criteria were missed. We believe that such gross errors are unlikely since at least one neuroradiologist and in total usually two radiologists evaluated all examinations as part of the clinical diagnostics. This being said, any patient missed would affect the reported frequency significantly due to the low prevalence of RIS. In terms of losses to follow-up, assuming that the frequency of RIS was the same in the 17 plausible RIS patients lost to follow-up as in those with all data available (1 case of RIS in 36 patients with plausible RIS), this would be equivalent to 1/36 x 17 = 0.47. This would increase the RIS frequency to 0.07%, or double the reported frequency to 0.1%, if rounded up to one patient. It is also unexpected that no elderly patients were classified as RIS since the presence of asymptomatic white matter lesions increase with age.[33] This might be due to the clinical information being available in the screening process, making it more likely to classify these

white matter changes as ischemic-degenerative. The study period was chosen to be the year 2001 in order to be able to show the natural long-term prognosis for the RIS cases identified with a potential follow-up period of 11 years. The reasoning for this was that regarding the published RIS cohorts, especially the retrospective cohorts, it is often unclear how the patients were initially identified. The hypothesis was therefore that patients with RIS that do not progress clinically are less likely to be noticed in the clinical setting, decreasing the chance of being included in a cohort, giving the observed cohort a worse prognosis. The study design did unfortunately not prove very helpful since only one case was identified, which limits the possibility of studying the prognosis. Although the study was conducted in 2001, it was conducted on modern 1·5 T MRI machines why the low frequency of RIS findings is hardly explained by technical reasons.

In conclusion this study suggest that RIS, according to present stringent criteria, is an uncommon finding in a tertiary hospital setting in a region with a high prevalence of MS. In order to more accurately determine the frequency of RIS in relation to MS prevalence, non-selected populations in large prospective studies actively involving both radiologists and neurologists are needed. In order to be able to study the prognosis of these patients large multi-center studies or case-control studies are recommended.

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FOOT NOTES

Contributors

TG initiated the study, designed data collection tools, performed the screening of all MRI examinations, monitored data collection, and drafted the paper. He is guarantor. JM performed neuroradiological image analysis. TG, JM, MKW, PA and SF all conceived and designed the study, analysed the data, and revised the paper.

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Competing interests

SF has received honoraria for lectures or educational activities from Allergan, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. All other authors declare no competing interests.

Ethics approval

This study was conducted with the approval of the regional ethical review board in Stockholm at Karolinska Institutet.

Patient consent

Obtained.

Data sharing statement

No additional data are available.

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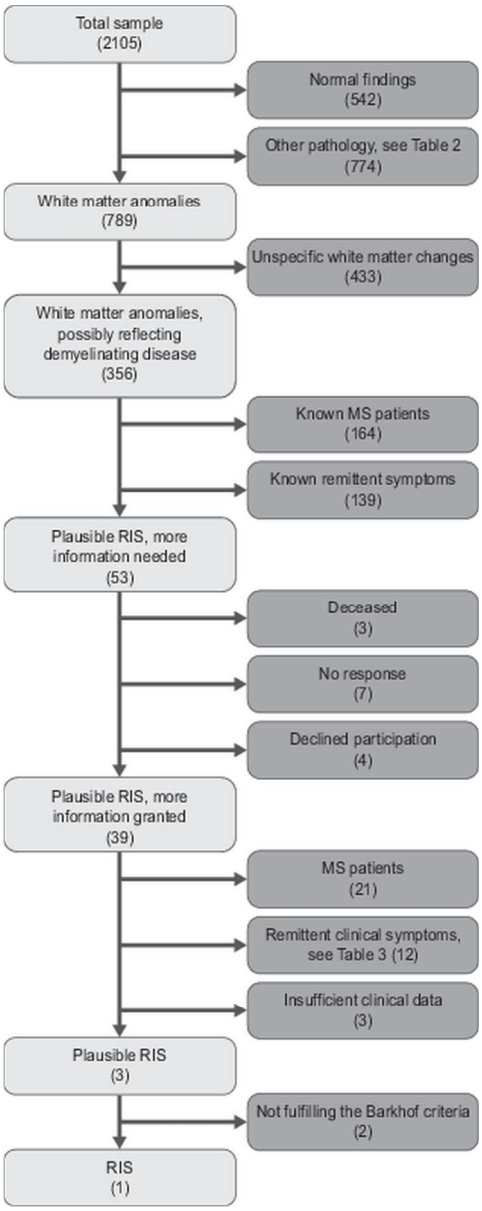
Figure 1

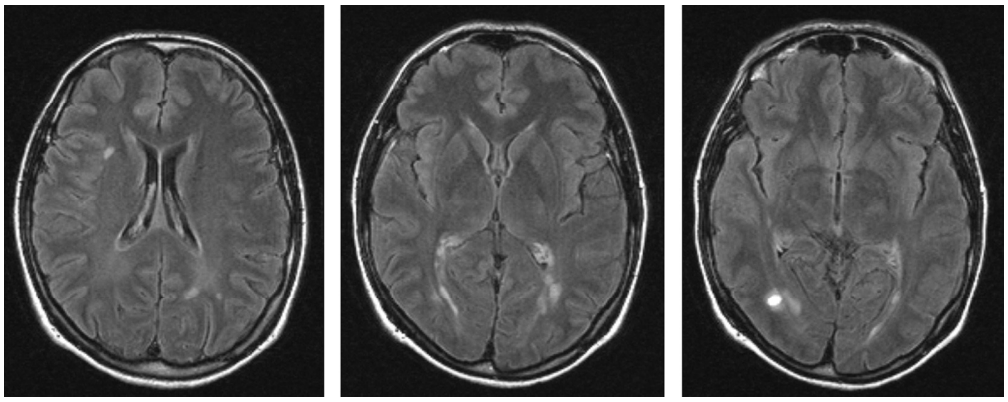
Flow chart of the screening process to identify patients with possible RIS

Figure 2

Axial FLAIR images of the identified RIS patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image



Flow chart of the screening process to identify patients with possible RIS
90x227mm (300 x 300 DPI)



Axial FLAIR images of the identified RIS patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image
173x67mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.