Cortical lesions in radiologically isolated syndrome

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ABSTRACT

Objective: To assess the presence of cortical lesions (CLs) as detected by MRI in subjects with radiologically isolated syndrome (RIS).

Methods: Fifteen subjects with RIS underwent an MRI examination, including a double inversion recovery sequence for CL assessment. T2-hyperintense white matter (WM) lesion volume (LV) and normalized volumes of brain and cortex were also obtained.

Results: Thirty-four CLs were identified in 6 of 15 (40%) subjects with RIS and predominantly distributed in frontotemporal lobes. CLs were frequent in subjects with RIS with immunoglobulin G oligoclonal bands on CSF, cervical cord lesions, and dissemination in time on brain MRI. WM LV was higher in subjects with CLs than in those without CLs (11.5 ± 10.1 vs 3.9 ± 2.8 cm^3, $p = 0.04$). Indeed, CL number and volume correlated with WM LV ($r = 0.57$, $p = 0.03$ and $r = 0.61$, $p = 0.01$). All subjects with CLs were classified in a previous study as having a very high probability of having relapsing-remitting multiple sclerosis (MS) on a logistic regression analysis of quantitative MRI indices.

Conclusions: We found CLs in subjects with RIS, a condition characterized by the unanticipated MRI finding of WM lesions highly suggestive of MS in the absence of a clinical scenario. CLs were mainly localized to the frontotemporal lobes and were associated with important markers of evolution to MS. ***Neurology***® **2011;77:1896–1899**

GLOSSARY

CI = cognitive impairment; **CIS** = clinically isolated syndrome; **CL** = cortical lesion; **DIR** = double inversion recovery; **DIT** = dissemination in time; **GM** = gray matter; **IgG** = immunoglobulin G; **LV** = lesion volume; **NBV** = normalized volume of brain; **NCV** = normalized volume of cortex; **RIS** = radiologically isolated syndrome; **WM** = white matter.

Because of the increasing use of MRI, a new condition named radiologically isolated syndrome (RIS) has recently emerged.[1] This condition refers to unanticipated brain spatial dissemination of MRI lesions highly suggestive of multiple sclerosis (MS) in the absence of a clinical scenario. However, whether subjects with RIS can be considered as having presymptomatic MS is still a matter of debate. Two very recent studies have provided important clues to this relevant issue, showing that the anatomic location of the lesions and their relative tissue damage could help in discriminating subjects with RIS who have a high likelihood of developing MS.[2,3]

In recent years, histopathology studies have shown extensive focal demyelination in the cortical gray matter (GM) of patients with MS.[4] A substantial number of these cortical lesions (CLs) can be imaged in vivo using advanced MRI techniques such as double inversion recovery (DIR)[4] or multisequence imaging protocols.[5] Thus, several studies have shown that CLs are a prominent feature in patients with MS from the earliest disease stages,[4] leading to the conclusion that this is an aspect that needs to be considered in the diagnostic workup of patients with clinically isolated syndrome (CIS) suggestive of MS.[6]

Against this background, we used DIR MRI acquisition to assess whether CLs could be detected in subjects with RIS.

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Table 1 Demographic and clinical characteristics of subjects with RIS

Subject no.	Sex	Age, y	Family history of MS	Age at first brain MRI, y	Reason for first brain MRI	Spinal cord MRI[a]	Time from first brain MRI, y	DIT on brain MRI	CSF[b]	CI index score[c]
1	M	46	No	44	Depression	−	2	−	−	16[d]
2	F	44	No	43	Anxiety	NP	1	−	+	8
3	F	53	No	50	Cervical trauma	+	3	+	+	16[d]
4	M	38	No	35	Dermatitis	−	3	−	−	0
5	M	45	Yes	42	Neuropathic pain	−	3	+	−	9
6	F	42	No	40	Dizziness (<2 min)	−	2	−	−	1
7	F	49	Yes	40	MS family history	+	9	−	NP	3
8	F	26	No	21	Pituitary adenoma	+	5	+	+	2
9	M	33	Yes	29	Headache	−	4	+	−	NP
10	F	40	No	31	Migraine with aura	−	9	+	+	5
11	F	24	No	22	Migraine without aura	+	2	+	+	4
12	F	35	No	34	Neck pain	+	1	+	+	6
13	M	48	No	45	Headache	NP	3	−	NP	1
14	F	20	No	19	Headache	+	1	+	+	3
15	F	32	No	28	Obesity	−	4	+	+	6

Abbreviations: CI = cognitive impairment; DIT = dissemination in time; MS = multiple sclerosis; NP = not performed; RIS = radiologically isolated syndrome.
[a] +, presence of cervical spine lesion; −, absence of signal abnormalities.
[b] +, presence of oligoclonal bands or abnormal immunoglobulin G index; −, normal pattern.
[c] The CI index score was obtained, as described previously[10], by a grading system applied to each subject's score on every cognitive test of the Rao Brief Repeatable Battery, dependent on the number of SDs from the mean normative values.
[d] Subjects with CI.

METHODS Fifteen asymptomatic subjects fulfilling the criteria for RIS[1] were included in the study. Table 1 reports their clinical and demographic features. They were all part of a previously studied RIS cohort.[3]

The study included 1) an MRI examination (without injection of contrast agent), 2) a full neurologic examination, which was independently performed by 2 experienced neurologists (E.P. and M.P.A.), to further exclude signs of CNS dysfunction, and 3) neuropsychological testing through the Rao Brief Repeatable Battery (with failure of at least 2 tests defining cognitive impairment [CI]).[3]

The brain MRI examination included conventional proton density, T2-weighted and T1-weighted sequences (50 slices, 3-mm thickness), and a DIR sequence (repetition time = 11,000 msec; echo time = 25 msec; inversion time 1 = 325 msec; inversion time 2 = 3,400 msec, 3-mm thickness). Images were acquired at the magnetic resonance center of the University of Siena using a 1.5-T scanner (Philips Medical Systems, Best, the Netherlands).

All CLs were identified on DIR images by consensus of 3 observers (A.G., M.L.S., and F.R.) who were blinded to subject identity. A senior neuroimaging expert (N.D.S.) was the arbiter in controversial cases. CLs were defined as focal hyperintensities entirely or partly located in the cortical GM, in accordance with recently published consensus recommendations.[7] T2-hyperintense white matter (WM) lesions were identified on proton density/T2-weighted images.

Normalized volumes of brain (NBV) and cortex (NCV) were measured on T1-weighted images by using the software SIENAX, part of FSL. To avoid tissue misclassification due to WM lesions, the latter were masked out and refilled with intensities matching the surrounding normal-appearing WM before tissue class segmentation analysis.

Comparisons between subjects with RIS with and without CLs were performed with the Mann-Whitney test. Correlations of CLs with MRI features were done with the Spearman coefficient. $p < 0.05$ was considered for statistical significance.

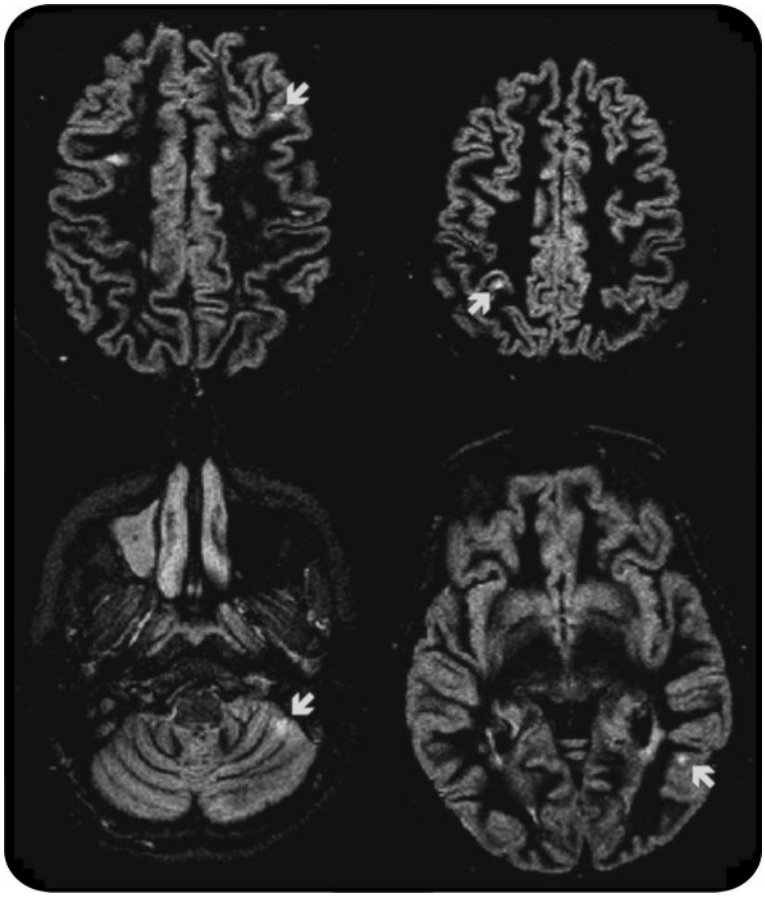
Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee, and informed written consent was obtained from all subjects before study entry.

RESULTS We identified a total of 34 round/ovoid CLs in 6 of 15 subjects with RIS (figure, table 2). With use of the previously proposed scoring recommendations,[7] full agreement among the 3 observers was reached in most cases (30 of 34 CLs, 88%).

The CL type was leukocortical (i.e., mixed GM-WM) (n = 15) and intracortical (n = 19). CLs were distributed predominantly in the frontal (n = 14) and temporal (n = 9) lobes, were less frequent in the parietal lobe (n = 6), and were sporadically found in the occipital lobe (n = 3) and cerebellar cortex (n = 2).

The presence of CLs was frequent in subjects with RIS with immunoglobulin G (IgG) oligoclonal bands on CSF (5 of 5 of those who underwent CSF analysis), cervical cord lesions (4 of 5 of those who

Figure Examples of cortical lesions (CLs) on double inversion recovery (DIR) in subjects with radiologically isolated syndrome (RIS)



Arrows identify CLs on DIR images in subjects with RIS. Images are shown in radiologic convention.

underwent spinal imaging), and dissemination in time (DIT) on brain MRI (5 of 6). Moreover, CLs were found in 1 of the 2 subjects with RIS (subjects 1 and 3) with CI (details in tables 1 and 2).

There were no differences in age, sex, CI index score, NBV, NCV, and T2-hyperintense WM lesion number ($p > 0.10$ for all) between subjects with RIS with and without CLs. However, WM lesion volume (LV) was higher in subjects with CLs than in those without CLs (11.5 ± 10.1 vs 3.9 ± 2.8 cm^3, $p = 0.04$). Indeed, CL number and volume correlated with WM LV ($r = 0.57$, $p = 0.03$ and $r = 0.61$, $p = 0.01$, respectively), whereas correlation of CL number with WM lesion number was $r = 0.42$, $p = 0.12$.

DISCUSSION We assessed here for the first time the presence of CLs in subjects with RIS. They were found in 40% of our asymptomatic subjects, mainly located in the frontal and temporal lobes. The occurrence of CLs in our RIS cohort was similar to that previously found by DIR imaging in patients with CIS suggestive of MS.[4,6] The predilection of CLs for frontal and temporal lobes was consistent with histopathology and MRI studies in MS.[4,8] Taken together, these data indicate that CLs are relevant in subjects with RIS, suggesting that in individuals with incidental WM lesions on MRI, the presence of CLs can increase the confidence for the attribution of the imaging findings to the spectrum of demyelinating diseases.

Whether the occurrence of CLs in RIS can be interpreted as an indicator of possible clinical evolu-

Table 2 MRI features of subjects with RIS

Subject no.	CL, n	CL volume, cm^3	T2-hyperintense WM lesions, n	T2-hyperintense WM LV, cm^3	NBV, cm^3	NCV, cm^3
1	0	0	15	1.9	1,557	530
2	0	0	22	4.3	1,390	520
3	11	0.79	23	30.4	1,252	440
4	0	0	29	4.3	1,418	526
5	0	0	14	3.4	1,477	521
6	0	0	25	3.6	1,436	551
7	0	0	12	1.8	1,478	540
8	8	0.47	41	7.8	1,557	604
9	0	0	15	10.9	1,479	551
10	0	0	22	3.3	1,400	496
11	0	0	12	1.8	1,487	580
12	6	0.51	22	13.7	1,530	604
13	3	0.16	10	2.7	1,518	570
14	2	0.46	27	10.8	1,462	578
15	4	0.14	34	3.7	1,448	552
Mean ± SD	2.3 ± 3.5	0.17 ± 0.26	21.5 ± 8.8	7 ± 7.5	1,460 ± 77	544 ± 42

Abbreviations: CL = cortical lesion; LV = lesion volume; NBV = normalized brain volume; NCV = normalized cortical volume; RIS = radiologically isolated syndrome; WM = white matter.

tion to MS cannot be established here. However, the finding that all subjects with RIS who showed CLs had IgG oligoclonal bands on CSF and that most of them had cervical lesions on spinal MRI and lesion DIT on brain MRI suggests a clinically relevant link between CLs and these important markers of evolution to MS.[2,3] Moreover, it is noteworthy that all 6 subjects with RIS with CLs were classified in a previous study as having a very high probability of having relapsing-remitting MS on a logistic regression analysis based on quantitative MRI indices.[3]

Our subjects with RIS with CLs had higher WM lesion volumes than those without CLs, as found in previous MS studies.[4] Thus, as in patients with MS, the presence of focal cortical demyelination seems to be related to the demyelinating/inflammatory process of the WM.

In contrast, CLs were not related to more pronounced cortical atrophy or worse cognitive performance (as assessed by a cognitive index score) (table 1). This finding is in line with the notion that global cortical atrophy is not directly related to focal CLs. However, our dataset is too small to allow for firm and general conclusions on this important matter.

Possible limitations to our study are 1) the already mentioned relatively small cohort of subjects with RIS, 2) the use of a 1.5-T scanner rather than the more sensitive 3-T scanner[9], and 3) the fact that a large proportion of CLs, especially subpial lesions, cannot be detected by DIR imaging. Despite these limitations, our study demonstrates that CLs similar to those found in patients with MS can be found in a subgroup of subjects with RIS. This result demonstrates that the occurrence of CLs can be an early phenomenon in RIS and can contribute to improving the management of subjects with this new preclinical condition.

AUTHOR CONTRIBUTIONS

Dr. Giorgio: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Stromillo: analysis or interpretation of data, acquisition of data, study supervision. Dr. Rossi: analysis or interpretation of data, acquisition of data. Dr. Battaglini: analysis or interpretation of data, statistical analysis. Dr. Hakiki: study concept or design, acquisition of data. Dr. Portaccio: analysis or interpretation of data, acquisition of data. Dr. Federico: drafting/revising the manuscript. Dr. Amato: drafting/revising the manuscript, acquisition of data. Dr. De Stefano: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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DISCLOSURE

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REFERENCES

1. Okuda DT. Unanticipated demyelinating pathology of the CNS. Nat Rev Neurol 2009;5:591–597.
2. Okuda DT, Mowry EM, Cree BA, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology 2011;76:686–692.
3. De Stefano N, Stromillo ML, Rossi F, et al. Improving the characterization of radiologically isolated syndrome suggestive of multiple sclerosis. PLoS One 2011;6:e19452.
4. Calabrese M, Filippi M, Gallo P. Cortical lesions in multiple sclerosis. Nat Rev Neurol 2010;6:438–444.
5. Bagnato F, Yao B, Cantor F, et al. Multisequence-imaging protocols to detect cortical lesions of patients with multiple sclerosis: observations from a post-mortem 3 Tesla imaging study. J Neurol Sci 2009;282:80–85.
6. Filippi M, Rocca MA, Calabrese M, et al. Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. Neurology 2010;75:1988–1994.
7. Geurts JJ, Roosendaal SD, Calabrese M, et al. Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI. Neurology 2011;76:418–424.
8. Calabrese M, Battaglini M, Giorgio A, et al. Imaging distribution and frequency of cortical lesions in patients with multiple sclerosis. Neurology 2010;75:1234–1240.
9. Simon B, Schmidt S, Lukas C, et al. Improved in vivo detection of cortical lesions in multiple sclerosis using double inversion recovery MR imaging at 3 Tesla. Eur Radiol 2010;20:1675–1683.
10. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 2009;66:1144–1150.