Abstract

Background: the usefulness of performing a spinal cord (SC) MRI in all clinically isolated syndromes (CIS) is controversial.

Objective: to assess the value of SC lesions for predicting MS diagnosis and disability accrual in CIS.

Methods: concerning SC lesions and MS diagnosis (2010 McDonald), adjusted Cox regression analyses were performed in increasingly specific CIS groups: all cases (n=207), non-SC CIS (n=143), non-SC CIS with abnormal brain MRI (n=90), and non-SC CIS with abnormal brain MRI not fulfilling 2010 MS (n=67). For the outcome EDSS ≥3.0, similar analyses were performed in all cases (n=207), non-SC CIS (n=143), and SC CIS (n=64). Performance at two years was assessed for all outcomes.

Results: presence of SC lesions increased MS risk 2.0-2.6 times independently of factors like brain lesions. If considering lesion number, the risk ranged from 1.6-2.1 for one lesion to 2.4-3.3 for ≥2. SC lesions increased the short-term disability risk around fivefold, better demonstrated in non-SC CIS. SC lesions were very specific for evolution to MS and showed very high sensitivity for EDSS ≥3.0.

Conclusions: SC lesions are independent predictors of MS in all CIS and contribute to short-term disability accrual. SC MRIs in CIS could be useful to estimate their prognosis.

Introduction

Technical improvements have mitigated the challenges of spinal cord (SC) MRI,[1] leading to its routine acquisition in the diagnostic work-up of patients with clinically isolated syndromes (CIS) in some institutions. Besides, SC lesions can provide evidence of dissemination in space (DIS) in the 2010 McDonald criteria.[2] Nevertheless, some studies conclude that SC MRIs should be performed only when the presenting symptoms suggest a myelitis or when brain MRI findings are inconclusive for MS.[3-7] Furthermore, there is limited information regarding the predictive value of SC lesions on evolution to MS [8, 9], their added value at baseline for diagnosing MS,[8, 10, 11] and their role in disability accrual,[12, 13] particularly in non-SC CIS. Consequently, the usefulness of systematically performing a SC MRI at the time of a CIS is still considered controversial, especially in presentations other than myelitis.[14-16]

Therefore, our objective was to evaluate the added value of SC lesions in CIS for reaching a diagnosis of MS and predicting disability accrual.

Materials and Methods

Study cohort

This study was based on a longitudinal, open CIS cohort at the MS Centre, Vall d'Hebron University Hospital, Barcelona. Patients <50 years of age first seen within three months of disease onset were included.[17] Demographic data, CIS topography, and disability according to the Expanded Disability Status Scale (EDSS) were recorded at baseline. IgG oligoclonal bands (OCB) were

determined within the first three months. Follow-up was performed every 3-6 months assessing for relapses and the EDSS measured during stability periods.

Concerning MRI acquisition and analysis, baseline brain MRIs were performed within 3-5 months of disease onset and follow-up scans at one year and every five years. Before 2007, SC MRIs were done if the presenting symptoms suggested a myelitis and in all CIS thereafter. Scans were obtained at 3.0 Tesla (T) since 2010 and at 1.5 T previously. Brain sequences included dual echo T2-weighted fast spin-echo, transverse and sagittal T2-weighted FLAIR, and transverse T1-weighted spin-echo. The transverse T1-weighted sequence was repeated after gadolinium (Gd) injection (gadobutrol, 0.2 mmol/kg) in patients with lesions on T2-weighted images (T2WI). SC sequences included sagittal dual echo proton density/T2-weighted fast spin-echo, sagittal short-tau inversion-recovery (STIR) and, in patients with brain Gd T1-weighted sequences or SC lesions, a Gd-enhanced sagittal T1-weighted. Axial T2-weighted sequences covered segments showing abnormalities on the sagittal images or with suspected clinical involvement.

All sequences were acquired with a contiguous 3-mm section thickness. Each MRI scan, performed in the daily practice, was assessed by one of two experienced neuroradiologists blinded to clinical follow-up. In doubtful cases, the final analysis was based on their consensus opinion.

MRIs were considered abnormal if ≥1 lesion was observed. The number and location of lesions on T2WI, number of Gd-enhancing and new T2 lesions on brain MRI, as well as lesion number (0, 1, 2-3, >3) and presence of Gd enhancement on SC were scored.

Experimental design

From this cohort, 100 consecutive patients with baseline brain and SC MRI at 3.0 T and 107 at 1.5 T were identified between 2007 and 2012. Baseline demographic and clinical characteristics were compared (data not shown). There were no significant differences except for CIS topography due to a higher number of optic neuritis in the 3.0 T group [3.0 T: 43 (43.0%) vs. 1.5 T: 27 (25.2%), p=0.038]. Furthermore, in accordance to a previous study,[18] there were no significant differences in SC lesion detection between MRI scans at 3.0 and 1.5 T in the entire CIS cohort [39/100 (39.0%) vs. 54/107 (50.5%), p=0.124], in SC CIS [17/24 (70.8%) vs. 33/40 (82.5%), p=0.353], and in non-SC CIS [22/76 (28.9%) vs. 21/67 (31.3%), p=0.855]. Therefore, both groups were merged (n=207) for the analyses, keeping field strength as a covariate in survival models.

Statistical Analysis

Henceforth, the term “MS” may refer to either CDMS (clinical) or McDonald MS (clinical or radiological).

Descriptive statistics were performed on demographic and clinical variables.

Added value of SC lesions for MS diagnosis

To evaluate whether baseline SC assessment could be more useful in specific clinical practice scenarios, Kaplan-Meier ~~Meyer~~ curves and uni- and

multivariable Cox proportional hazards regression analyses were performed in the following increasingly specific groups according to presence vs. absence of SC lesions with 2010 McDonald MS [2] and CDMS [19] as the outcomes during the total follow-up time:

- All cases considering symptomatic and asymptomatic SC lesions
- Non-SC CIS regardless of brain MRI findings
- Non-SC CIS with abnormal brain MRIs irrespective of DIS and DIT fulfilment
- Non-SC CIS with abnormal brain MRI not fulfilling DIS and DIT

Multivariable survival analyses were adjusted by age, sex, CIS topography, OCB, T2 brain lesion number (0, 1-3, 4-9, ≥10), magnet field strength, and disease modifying treatment (DMT) (before CDMS, McDonald MS) as a time-dependent variable. A “missing” category was added for patients with no OCB determination. Results for multivariable analyses are expressed as adjusted hazard ratios (aHR).

A similar survival analysis was performed according to SC lesion number (0, 1, ≥2) for the two MS outcomes.

As a secondary objective, we studied the added value of SC MRI in the fulfilment of the 2010 McDonald criteria at baseline. Given SC MRIs are almost invariably performed in myelitis cases, we focused on the 143 (69.1%) non-SC CIS using the following approach: we determined the proportion of patients fulfilling an alternative criterion assessing the presence of ≥2/3 DIS criteria on baseline brain MRI, and then used both brain and SC MRI to evaluate the

presence of ≥2/4 DIS criteria, to finally determine how many patients fulfilled radiological DIS and DIT in each scenario. Afterwards, the number needed to scan (NNS) to diagnose one additional case was calculated.[8]

Added value of SC lesions for predicting disability accrual

Using EDSS ≥3.0 assessed from month 12 of follow-up as the disability outcome according to presence of SC lesions, Kaplan-Meier ~~Meyer~~ curves and uni- and multivariable Cox proportional hazards regression analyses were performed in:

- All cases (n=207)
- SC CIS (n=64)
- Non-SC CIS (n=143)

The multivariable survival analyses were adjusted by the previously mentioned covariates, considering DMT before EDSS ≥3.0.

In all Cox regression models, we evaluated the proportionality of hazards assumption using the Grambsch-Therneau test.

SC lesions' performance

We assessed the performance of baseline SC lesions (dichotomic variable) with the outcomes CDMS, 2010 McDonald MS, and EDSS ≥3.0 at two years in the previously mentioned groups. Sensitivity, specificity, accuracy, positive

predictive value (PPV), and negative predictive value (NPV), all with exact binomial 95% CI, were calculated.

Statistical tests were performed on the 0.05 level of significance using IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA), version 20.0.

This study received approval from the Clinical Research Ethics Committee at Vall d'Hebron University Hospital [PR(AG)174/2012]. All patients signed written informed consents.

Results

Baseline characteristics

Of all 207 patients, two thirds were female with a mean (SD) age of 32.6 (8.1) years. A SC CIS occurred in 30.9%. Regarding brain MRI, 65.2% had ≥1 lesion. The SC MRI demonstrated ≥1 lesion in 44.9% (78.1% SC vs. 30.1% non-SC CIS, $p<0.0001$) (Table 1). Figure 1 shows a representative non-SC CIS case with SC lesions.

Please insert Table 1 and Figure 1 here.

These baseline characteristics were comparable with the rest of the CIS cohort not selected for this study (n=807, data not shown), except for age [30.7 (8.2), p=0.004].

Outcome measures

During a mean follow-up of 35.7 (15.8) months, 29.5% of patients developed CDMS, 44.9% fulfilled the 2010 McDonald criteria, and 6.3% reached an EDSS ≥3.0. The median (percentiles 25-75 ~~IQR~~) time to CDMS was 8.7 (4.3-24.0) months, 4.7 (3.3-12.0) for McDonald MS, and 24.0 (12.0-36.0) for EDSS ≥3.0.

Results according to CIS topography (SC and non-SC) are shown in Table 1. The corresponding data for the other two CIS groups are shown in Annex 1.

Added value of SC lesions for MS diagnosis

When evaluating McDonald MS, Kaplan-Meier curves showed that patients with SC lesions had a higher risk of fulfilling this outcome in all groups (Figure 2). Moreover, when controlling for other variables, all the aHRs were significantly increased, between 2.0 and 2.6 times (Table 2).

Please insert Figure 2 and Table 2 here.

If considering SC lesion number, the aHRs ranged from around two-fold for one SC lesion to 2.4-3.3 for ≥2 lesions (Table 3).

Please insert Table 3 here.

Regarding CDMS, more patients with SC lesions reached this outcome than those with no lesions (Figure 3). Presence of SC lesions posed an increased risk for CDMS in all 207 patients (aHR 1.9, 95% CI 1.03-3.6, p=0.041), losing significance as CIS groups became smaller (aHR 1.9, 95% CI 0.9-4.0, p=0.080 for all non-SC CIS). The HRs also increased along with lesion number, losing significance in the multivariable analyses (data not shown).

Please insert Figure 3 here.

As for the added value of SC MRI in the fulfilment of the 2010 McDonald criteria at baseline, the NNS decreased from 36 in all non-SC CIS to 17 in cases with abnormal brain scans not fulfilling DIS and DIT (Table 4).

Please insert Table 4 here.

Added value of SC lesions for predicting disability accrual

The presence of SC lesions was associated with a greater risk of reaching an EDSS ≥3.0, observed in 11/93 (11.8%) cases vs. 2/114 (1.8%) in the group

without SC lesions (p=0.003). We found no differences in the proportion of patients reaching an EDSS ≥3.0 according to CIS topography [6/64 (9.4%) SC vs. 7/143 (4.9%) non-SC, p=0.352]. The presence of SC lesions increased the risk of reaching an EDSS ≥3.0 when evaluating all 207 patients and was especially significant in non-SC CIS (Figure 4 and Table 5). In the SC CIS model we only introduced sex, age, and SC lesions as no cases were observed in the other covariates.

Please insert Figure 4 and Table 5 here.

We observed no deviation from proportionality after fitting all Cox models using the Grambsch-Therneau test (p from 0.3061 to 0.6648).

SC lesions' performance

Concerning McDonald MS at two years, presence of SC lesions showed a very good specificity and PPV, especially in non-SC CIS (Table 2).

Performance of SC lesions for CDMS showed a good specificity, especially in non-SC CIS groups (from 63.4% to 76.5%), with a good NPV in all groups (from 65.7% to 76.9%).

Finally, the presence of SC lesions was highly sensitive and had a very good NPV for EDSS ≥3.0 (Table 5).

Discussion

This study shows that the presence of SC lesions is an independent risk factor for reaching a diagnosis of MS regardless of other demographic or clinical-radiological factors. This effect was better demonstrated for McDonald MS possibly due to the higher number of patients reaching this outcome [2] compared to CDMS. Importantly, our analyses show that MS risk increases with a higher SC lesion number, better demonstrated in McDonald MS.

Other studies have evaluated the diagnostic role of SC lesions in CIS. Patrucco and colleagues studied 75 patients with typical CIS topographies and found a ≥3.5-fold risk for CDMS independently of brain lesions, OCB, and CIS topography.[9] Sombekke and colleagues assessed four CIS groups and found that presence of SC lesions conferred the highest CDMS risk in non-SC cases not fulfilling the MS criteria on brain MRI.[8] One important advantage in our study is the possibility to assess baseline demographic, clinical, CSF, and brain imaging data in differing multivariable models. Our results indicate that both presence and increasing number of SC lesions pose a two- to threefold risk for evolving to MS regardless of the initial brain MRI findings. These findings also suggest that not only lesion number, but also lesion location irrespective of the initial clinical presentation, may play a role in defining MS risk, as previously demonstrated with infratentorial lesions.[20, 21]

When evaluating the role of SC MRI on fulfilling the 2010 McDonald criteria at baseline, our results, compared to previous publications, suggest that criteria fulfilment may differ according to the studied population’s baseline findings. For instance, Sombekke and colleagues observed that only seven scans were

needed to diagnose one additional patient in a CIS cohort comprising 121 individuals with highly pathological baseline MRIs.[8] Conversely, Dalton and colleagues assessed 115 patients with optic neuritis, 27.0% of them with SC lesions, and found that SC MRI allowed the diagnosis in one additional patient at one year and in two at three years after applying the 2001 criteria.[10, 22] Finally, a study of 41 paediatric CIS showed the McDonald criteria were fulfilled through DIT in four additional patients when including the SC scan in the analysis.[11] In our cohort, the NNS improved by eliminating cases with normal brain MRIs and especially when assessing SC scans in patients with abnormal brain MRIs not fulfilling the diagnostic criteria. Nevertheless, if the criteria are not fulfilled at baseline even after adding the SC MRI findings, these patients still merit a close clinical-radiological monitoring if they presented a typical CIS and/or have suggestive lesions.[23]

As for the prognostic value of SC lesions in disability accrual, Swanton and colleagues evaluated 100 optic neuritis cases and observed that presence of SC lesions was a predictor for reaching a higher disability outcome (ranked EDSS: 0, 1, 1.5-2.0, ≥2.5) together with Gd-enhancing and new T2 lesions (OR 3.30, 95% CI 1.26-8.68). When evaluating SC lesion number (0, 1, 2, ≥3), SC lesions were predictors of disability together with infratentorial and new T2 lesions. And in patients who developed CDMS, the only predictor was presence or number of SC lesions.[12]

Brownlee and colleagues assessed 131 non-SC CIS with a median follow-up of 5.2 years, observing that SC measures such as baseline lesion number, change in lesion number and change in upper cervical cord cross-sectional area were independently associated with reaching an EDSS ≥3.0 (R^2=0.53), whereas

adding brain MRI data only modestly increased the model´s predictive value (R^2=0.64).[13]

In our study, we found that presence of SC lesions increases the risk of short-term disability accrual around fivefold, better demonstrated in non-SC CIS. That does not mean SC CIS patients have a lower risk of reaching this outcome. It could be argued that radiological demonstration of SC lesions in non-SC CIS may improve discriminating patients at higher risk of developing disability by providing additional information already demonstrated clinically in SC CIS. That the latter comprises the smallest group with only one patient without SC lesions affecting the survival analyses also may have played a role in our results. Therefore, our study is limited by the few patients reaching the disability outcome during our short follow-up. The significant results Swanton and colleagues found might be related not only to their longer follow-up, but also to their definition of disability, as ours is more restrictive. However, we also consider it a more robust outcome since inter-observer variability is high with lower EDSS scores and, from the clinical point of view, an EDSS of 3.0 represents moderate disability. One advantage of our study is the better representation of non-SC CIS topographies other than optic neuritis compared to the two aforementioned studies, with the latter having an overrepresentation of this topography (87%).[13] Unfortunately, we did not test SC lesion number due to the few patients reaching our outcome. Moreover, we did not assess the precise location of SC lesions in the transverse plane and, consequently, could not establish the relevance of gray matter involvement. Other sequences, such as high resolution phase sensitive inversion recovery, which can delineate the

gray/white matter boundaries on the axial plane, were not obtained due to the long acquisition time even with 3.0 T magnets.[24, 25]

Regarding SC lesion performance, our results confirm the high specificity they confer to MS diagnosis,[2, 22, 26-29] mostly in non-SC CIS and with McDonald MS as the outcome. This underscores their important role in the differential diagnosis of MS. Besides, their high PPV supports their usefulness for McDonald MS diagnosis in the clinical practice. Taking these results together with the regression analyses findings, our data indicates that both presence and number of SC lesions may further contribute to individualize MS risk.[17]

When considering performance at two years with EDSS ≥3.0 as the outcome, SC lesions were highly sensitive for disability accrual, while the high NPV, particularly in non-SC CIS, suggests the probability of reaching an EDSS ≥3.0 in the short-term is very low if no SC lesions are present. Therefore, the presented results support the notion that SC lesions might pose a higher risk for short-term disability. This implies that lesion topography could also be assessed to consider the use of highly effective DMTs, but specific studies on this subject are needed.[30]

Nonetheless, an important limitation of our work is the limited follow-up, hindering our disability analysis. Further studies, including a future reassessment of the present cohort, are required to confirm the prognostic role of baseline SC lesions in the medium- to long-term.

Other limitations include the small number of patients in several subgroups and the impossibility to assess the SC lesion number as thoroughly as in the brain due to the technical limitations. In fact, even in patients with myelitis, we

detected SC lesions in 78.0%, a finding explained by the limited sensitivity of MRI in depicting small and marginally located lesions, and because of movement or ghosting artefacts. However, the proportion of SC CIS patients with ≥1 SC lesion in our study is very similar to the percentage in a previous work.[8] Furthermore, presence or number of lesions may not portray the extent of the disease properly and other variables such as lesion volume or atrophy measures might be necessary, particularly when assessing disability.[1, 13, 31-33] Many of these techniques will aid in our understanding of MS, but it will be important to identify which will also be useful for assessing prognosis in the clinical practice.

Therefore, although from the diagnostic point of view the added value of SC MRI is moderate in the best-case scenario, SC lesions are independent, highly specific predictors of evolution to MS and lesion number is relevant. Importantly, SC lesions are an independent risk factor for short-term disability, better demonstrated in non-SC CIS in our cohort. Given these results indicate their value not only for diagnosis but potentially also for prognosis, further studies with larger cohorts and a longer follow-up are justified to help define patient groups in which a baseline SC MRI could be more valuable.

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Declaration of conflicting interests

Georgina Arrambide has received compensation for consulting services from Biogen-Idec, research support from Novartis, and speaking honoraria from Sanofi-Aventis.

Alex Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the *American Journal of Neuroradiology* and Neuroradiology, has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, OLEA Medical, Stendhal, Novartis and Biogen Idec, receives research support from Bayer, and has research agreements with Siemens AG.

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Joaquín Castilló declares that there is no conflict of interest.

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Ingrid Galán declares that there is no conflict of interest.

Breogán Rodríguez-Acevedo declares that there is no conflict of interest.

Luciana Midaglia declares that there is no conflict of interest.

Carlos Nos declares that there is no conflict of interest.

Patricia Mulero declares that there is no conflict of interest.

Maria Jesús Arévalo declares that there is no conflict of interest.

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Xavier Montalban has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Amirall, Bayer, Biogen, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi-Genzyme and Teva Pharmaceutical.

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