**Clinico-radiological dissociation of disease activity in MS patients: frequency and clinical relevance**

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**Article type:** Original communication

**Word count:** **Abstract:** 270 words

**Manuscript:** 1333 words

**References:** 12

**Figures:** 1

**Tables:** 1

**Keywords:** Multiple sclerosis, MRI, clinically isolated syndrome

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**ABSTRACT**

**Objective**

To investigate the prevalence and clinical relevance regarding disability progression in multiple sclerosis patients with a dissociation in clinical and radiological disease expression.

**Methods**

We prospectively selected patients with early relapsing-remitting MS or a clinically isolated syndrome (CIS) from the Amsterdam MS cohort. Patients underwent clinical examination at baseline, after 2 years, 6 years and a subset also after 11 years, including the Expanded Disability Status Scale (EDSS), 25-foot walk test (25-FWT) and 9-hole peg test (9-HPT). Brain and spinal cord MRI scans were obtained at baseline and after 2 years. Two years after baseline, patients with dissociation in their clinical and radiological disease progression were identified as: 1) patients with high clinical disease activity (defined by relapses) and low radiological disease activity (defined by white-matter lesions on T2-weighted imaging); or 2) patients with low clinical disease activity and high radiological disease activity. Binary logistic regression analyses were performed to predict disability progression after 6 and 11 years of follow-up. Patients with low clinical and low radiological disease activity were used as the reference group.

**Results**

The prevalence of clinico-radiological dissociation was low (6.4% had high clinical and low radiological disease activity and 5.1% had a combination of low clinical and high radiological disease activity) compared to 88.5% of patients without a dissociation. Patients with or without a dissociation of clinical and radiological disease activity did not show a statistically significant difference in risk of disability progression after 6 and 11 years.

**Conclusions**

A clinico-radiological dissociation is rather a rare phenomenon in MS patients. The clinical relevance of such a dissociation regarding the prediction of disability progression is questionable.

## INTRODUCTION

Clinical and magnetic resonance imaging (MRI) outcome measures (e.g., relapses/disability and lesion load/active MS lesions, respectively) are routinely used for prognostic and disease monitoring purposes in multiple sclerosis (MS).[1] Several studies demonstrated a rather limited correlation between clinical and imaging outcome measures in terms of MS disease progression coining the term 'clinico-radiological paradox'.[2] However, as a consequence of the inconclusive definition of the term 'clinico-radiological paradox', data concerning the prevalence of dissociation in clinical and radiological disease activity is lacking. In addition, little is known about disability progression in these patients. In general, disability progression varies considerably between MS patients and early recognition of patients with a less favorable outcome could support in decision making for treatment options.[3]

The aim of this study was to determine the prevalence of dissociation in clinical and radiological disease activity in MS and explore the risk of disability progression in these patients.

## METHODS

For this prospective study, we selected patients with an early course of relapsing-remitting MS or a clinically isolated syndrome (CIS) diagnosed according to the 2005 revisions of the McDonald criteria.[4] Details about this cohort have been described previously.[5] We included patients who visited the hospital within 18 months after symptom onset and were aged between 18 and 60 years at onset. MRI data of brain and spinal cord had to be available at baseline and after 2 years of follow-up, even as clinical data at baseline and after 2 and 6 years of follow-up.

Patients underwent clinical examination at baseline, after 2 years, 6 years and a subset also after 11 years, including the Expanded Disability Status Scale (EDSS), 25-foot walk test (25-FWT) and 9-hole peg test (9-HPT). Brain and spinal cord MRI scans were obtained at baseline and after 2 years. The imaging protocols have been described previously.[5]

Patients were classified into groups based on clinical and radiological disease activity during the first 2 years of the disease. Clinical disease activity was defined as the annualized relapse rate (ARR) and radiological disease activity as the number of new T2-hyperintense lesions in the brain and spinal cord per year. To calculate the ARR, relapses were recorded from onset to the 2-year visit and annualized. Relapses were counted by medical records and patient self-reporting of symptoms before baseline visit. Cut-off values for high and low clinical and radiological disease activity were based on the first and third tertile of clinical or radiological disease activity and the thresholds for ARR and new T2 hyperintense lesions per year are reported in Figure 1. Patients were labeled as having a 'dissociated disease' if they met the criteria for high clinical disease activity combined with low radiological disease activity (HC/LR) or a combination of low clinical disease activity and high radiological disease activity (LC/HR). To create a homogeneous reference group, patients with low clinical and radiological disease activity (LC/LR) were used as the reference group.

Disability progression was defined as an increase in 6- or 11-year EDSS scores of 1.5, 1 or 0.5 in case of a baseline EDSS score of 0, 1-5.5 or ≥ 6.0, respectively.[6] EDSS-plus progression (progression on the EDSS or an increase of ≥20% in time on the 25-FWT or 9-HPT) was also determined.[7]

Statistical analyses were performed using IBM SPSS statistics version 22.0. Binary logistic regression analyses were performed to predict disability progression after 6 and 11 years of follow-up. All analyses were corrected for baseline EDSS. Outcomes were assumed significant for *p*-values ≤0.05. We did not correct the analysis with respect to the use of DMTs (yes/no) because the use of DMT was not a confounder. In addition, we did not correct the analysis for the use of any specific treatments because the spectrum of DMTs is large and the size of the cohort is too small for any correction in the analysis.

**RESULTS**

A total of 157 MS patients were included in this study. Baseline demographic, clinical and radiological characteristics and the risk of disability progression are summarized in Table 1. Figure 1 shows the cut-off values for high and low clinical and radiological disease activity. Ten patients (6.4%) had HC/LR disease activity and eight patients (5.1%) had LC/HR disease activity. A total of 139 patients (88.5%) did not have a dissociated disease of which 23 patients (14.7%) met the criteria for LC/LR disease activity and 29 patients (18.5%) had HC/HR disease activity. Except for EDSS and lesion number on MRI, no differences in baseline characteristics were found between the groups.

Patients with a dissociated disease (HC/LR and LC/HR) did not statistically differ regarding their risk of disability progression after 6 and 11 years. Essentially, the risk of disability progression after 6 and 11 years did not statistically differ between the dissociated groups (HC/LR and LC/HR) and the reference group (LC/LR) (Table 1, lower panel).

**DISCUSSION**

The so-called clinico-radiological paradox in MS patients is frequently considered as a clinically relevant phenomenon.[2,8] In this study, we determined the prevalence of a dissociation in clinical and radiological disease activity and the risk of disability progression for these patients. Identifying patients with a more unfavorable outcome early in the disease is of great importance since it could aid in decision making for treatment options and providing a more individualized treatment. To our knowledge, this is the first study assessing dissociated disease activity in MS patients with a longitudinal follow-up and measuring radiological disease activity by both brain and spinal cord lesions.

A dissociation in clinical and radiological disease activity, according to our definition, was relatively infrequent in our cohort.[8] Of the 157 included patients, 18 patients (11.5%) showed a dissociated disease comprising 10 patients with HC/LR disease activity and 8 patients with LC/HR disease activity.

The clinical consequence of a dissociated disease in MS patients seemed to be limited based on our study. The risk of EDSS progression or EDSS-plus progression after 6 and 11 years did not statistically differ between patients with a dissociation in disease activity and the reference group.

A recent cross-sectional study assessed whether patients with a dissociation between lesion volume and disability were more vulnerable to a progressive disease course compared to patients with a non-dissociated disease.[8] In line with our results, the prevalence of a dissociated disease was low: only 4.1% showed a combination of low lesion volume and high disability and 9.4% had high lesion volume and low disability scores. They showed that patients with HC/LR disease activity were more likely to have a progressive disease course.[7] Since both high relapse rates [9,10] and high T2 lesion loads have been shown to predict future disability,[10,11] we could speculate that a dissociation with either high relapses or high T2 lesion load could result in a higher risk of disability progression.

An important limitation of this prospective study has to be addressed. As a result of the fact that the phenomenon is seemingly quite rare, the limited sample size prevents drawing firm conclusions on the risk of disability progression. A potential limitation is the inclusion of exclusively inflammatory imaging markers and no advanced MRI measures and markers of neurodegeneration (e.g., atrophy, T1-hypointense lesions) in our analysis. There are considerable reasons for this. First of all, the term “clinico-radiological” was derived from data dealing with inflammatory imaging markers.[2] In addition, the focus was on a situation that reflects clinical routine practice. Quantitative and volumetric MRI measures are not used in clinical routine on regular basis as recommended by recent guidelines.[12]Future research should include a larger, possibly multicenter patient population and it would be interesting to also consider quantitative imaging measures such as atrophy or connectivity and further develop the relation between MRI measures and clinical outcome including cognitive measures.

**CONCLUSION**

A clinico-radiological dissociation is rather infrequently observed in MS patients. The clinical relevance of this dissociation is still a topic of debate since – even though we could not detect significant differences – dissimilarities in the risk of disability progression cannot be fully excluded. The low prevalence of dissociation requires larger patient groups to confirm the predictive value for disability progression.

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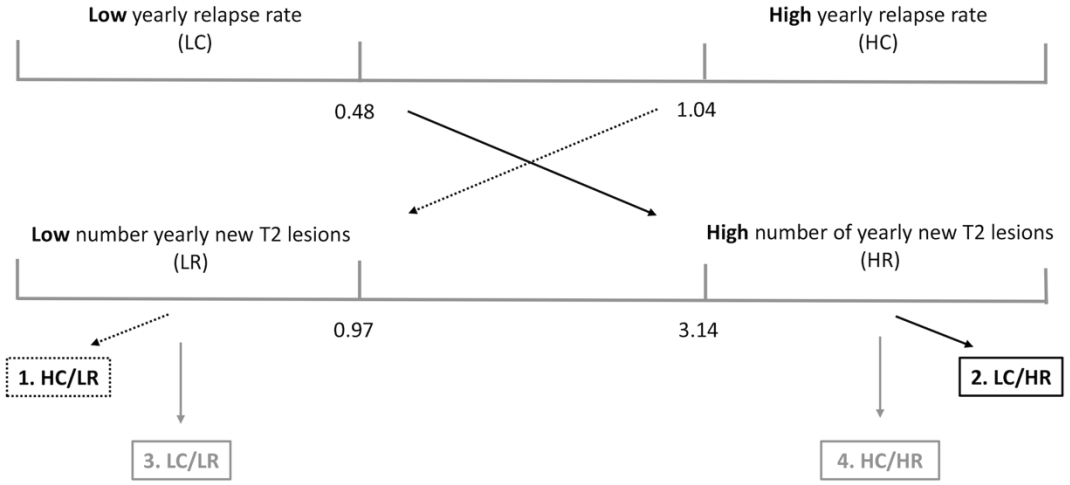


**Figure 1. Visualization of the definitions for dissociation in clinical and radiological disease activity.**

Figure 1 visualizes the classification of patients according to their clinical and radiological disease activity. HC: high clinical disease activity (annualized relapse rate over first 2 years); HR: high radiological disease activity (number of new T2 lesions over first 2 years); LC: low clinical disease activity (annualized relapse rate over first 2 years); LR: low radiological disease activity (number of new T2 lesions over first 2 years); LC/LR: low clinical and low radiological disease activity; LC/HR: low clinical and high radiological disease activity; HR/LR: high clinical and low radiological disease activity, HC/HR: high clinical and high radiological disease activity.

**Table 1. Patients characteristics and risk of disability progression**

| **Baseline** | ***All patients (n=157)*** | **HC/HR (n=29; 18.5%)** | **HC/LR (n=10; 6.4%)** | **LC/HR (n=8; 5.1%)** | **LC/LR (n=23; 14.7%)** |
|---|---|---|---|---|---|
| *Clinical characteristics* | | | | | |
| Age (mean, SD)[a] | *34.5 (9.0)* | 28.8 (6.8)[w] | 36.8 (7.1) | 35.4 (9.4) | 37.7 (9.6) |
| Sex (n, % female)[b] | *105 (66.9)* | 18 (62.1) | 8 (80.0) | 5 (62.5) | 13 (56.5) |
| Disease duration at baseline, years (mean, SD)[a] | *0.6 (0.3)* | 0.5 (0.3) | 0.7 (0.3) | 0.5 (0.2) | 0.6 (0.3) |
| EDSS (median, IQR)[c] | *2.0 (1.5-3.0)* | 2.0 (1.5-2.5) | 2.5 (2.0-4.0)[x,y] | 2.0 (1.5-3.0)[x] | 2.0 (1.0-3.0)[y] |
| 25-FWT (mean, SD)[a] | *4.1 (1.3)* | 4.0 (0.5) | 5.2 (2.3) | 3.7 (0.5) | 4.0 (2.0) |
| 9-HPT (mean, SD)[a] | *18.0 (3.3)* | 18.2 (2.7) | 19.8 (5.1) | 17.0 (1.9) | 18.5 (5.8) |
| *Baseline MRI characteristics* | | | | | |
| Brain | | | | | |
| No. T2-hyperintense lesions (median, IQR)[c] | *13 (6-25)* | 19 (12-39)[w] | 10 (2-19) | 25 (9-62)[z] | 5 (2-11)[z] |
| No. T1 Gd+ lesions (median, IQR)[c] | *0 (0-1)* | 2 (0-4)[w] | 1 (0-3) | 1 (0-4) | 0 (0-0) |
| Spinal cord | | | | | |
| No. T2-hyperintense lesions (median, IQR)[c] | *1 (0-4)* | 4 (1-9)[w] | 1 (0-2) | 1 (0-4) | 0 (0-1) |
| No. T1 Gd+ lesions (median, IQR)[c] | *0 (0-0)* | 1 (0-2)[w] | - | - | 0 (0-0) |

| **Follow-up** | ***All patients*** | **HC/HR** | **HC/LR** | **LC/HR** | **LC/LR** |
|---|---|---|---|---|---|
| *6-year (n)* | *157* | 29 | 10 | 8 | 23 |
| Follow-up length, years (mean, SD)[a] | *5.9 (0.9)* | 6.1 (1.0) | 5.6 (0.9) | 5.9 (1.2) | 5.7 (0.9) |
| DMT-use (n, %)[b] | *85 (54.1)* | 25 (86.2)[w] | 8 (80.0)[y] | 4 (50.0) | 6 (26.1)[y] |
| EDSS progression (n, %)[b] | *56 (35.7)* | 12 (41.4) | 3 (30.0) | 1 (12.5) | 8 (34.8) |
| EDSS-plus progression (n, %)[b] | *65 (48.1), (n=135)* | 13 (59.1) | 5 (55.6) | 3 (42.9) | 11 (50.0) |
| *11-year (n)* | *97* | 18 | 5 | 7 | 14 |
| Follow-up length, years (mean, SD)[a] | *11.4 (1.7)* | 11.6 (1.3) | 10.2 (1.6) | 11.0 (2.2) | 11.8 (2.1) |
| DMT-use (n, %)[b] | *59 (60.8)* | 15 (83.3) | 4 (80.0)[y] | 5 (71.4) | 4 (28.6)[y] |
| EDSS progression (n, %)[b] | *51 (52.6)* | 9 (50.0) | 2 (40.0)[x] | 2 (28.6)[x] | 6 (42.9) |
| EDSS-plus progression (n, %)[b] | *58 (67.4), n=86* | 11 (64.7) | 2 (40.0) | 5 (100) | 10 (71.4) |

| Risk of disability progression | n | Odds ratio (95% CI) | *p*-value |
|---|---|---|---|
| *HC/LR vs LC/HR* | | | |
| EDSS progression 6-year FU | 18 | 1.8 (0.12 – 27.26) | 0.67 |
| EDSS-plus progression 6-year FU | 16 | 1.2 (0.15 – 10.55) | 0.83 |
| EDSS progression 11-year FU | 12 | 2.2 (0.16 – 28.79) | 0.56 |
| EDSS-plus progression 11-year FU | 10 | - | - |
| | | | |
| *HC/LR vs LC/LR* | | | |
| EDSS progression 6-year FU | 33 | 1.6 (0.25 – 10.20) | 0.62 |
| EDSS-plus progression 6-year FU | 31 | 2.1 (0.37 – 11.95) | 0.40 |
| EDSS progression 11-year FU | 19 | 1.7 (0.16 – 18.28) | 0.65 |
| EDSS-plus progression 11-year FU | 19 | 0.35 (0.04 – 3.24) | 0.36 |
| | | | |
| *LC/HR vs LC/LR* | | | |
| EDSS progression 6-year FU | 31 | 0.36 (0.03 – 3.74) | 0.39 |
| EDSS-plus progression 6-year FU | 29 | 0.85 (0.15 – 4.87) | 0.85 |
| EDSS progression 11-year FU | 21 | 0.66 (0.09 – 5.11) | 0.69 |
| EDSS-plus progression 11-year FU | 19 | - | - |

*CI: confidence interval; DMT: disease modifying treatment; EDSS: Expanded Disability Status Scale; FU: follow-up; Gd+: gadolinium enhancing; HC/LR: high clinical – low radiological disease activity group; IQR: interquartile range; LC/HR: low clinical – high radiological disease activity group; LC/LR: low clinical – low radiological disease activity group; n: number of patients; SD: standard deviation; 25-FWT: 25-foot walk test; 9-HPT: 9-hole peg test.*

*[a] Independent samples t-test, [b] Pearsons chi-square test, [c] Mann-Whitney U test.*
*[w] Significant differences between HC/HR and LC/LR group, [x] significant differences between HC/LR and LC/HR group, [y] significant differences between HC/LR and LC/LR group, [z] significant differences between LC/HR and LC/LR group. Significance was set at a p-level <0.05.*

Table 1 shows the patient characteristics per group for baseline and follow-up. The lower panel shows the risk of disability progression per group. All prediction models were corrected for baseline EDSS.

**DECLARATIONS**

**Availability of data and material:** data was transparent for all authors

**Code availability:** software application

**Ethics approval:** The study was approved by the Institutional review board of the VU University Medical Center, Amsterdam, The Netherlands

**Consent to participate:** Written informed consent was obtained from all participants for the use of the clinical, laboratory and imaging data for research and teaching purposes.

**Consent for publication:** Written informed consent was obtained from all participants for publishing the data.

**Potential conflicts of interest**

**N. van Faals, L.J. Balk, B. Moraal** have nothing to disclose. **I. Dekker** received speaking honoraria from Roche. **F. Barkhof** serves as editorial board member of Brain, Neuroradiology, Neurology, Multiple Sclerosis Journal and Radiology. He has accepted personal fees from Springer, Bayer, Biogen, Roche, Apitope Ltd, IXICO ltd, Novartis, GeNEuro. Grants from Novartis, TEVA, Merck, Biogen, IMI-EU, GE Healthcare, UK MS Society, Dutch MS research foundation, NWO, NIHR. FB is supported by the NIHR UCLH biomedical research centre. **B.M.J. Uitdehaag** has received consultancy fees and/or research support from Biogen Idec, Sanofi Genzyme, Merck Serono, Roche and Teva. **J. Killestein** reports grants and personal fees from Biogen Idec, Novartis, Merck Serono, TEVA, Genzyme, Roche, outside the submitted work. **M.P. Wattjes** reports personal consultancy and speaking fees from Biogen, Novartis, Janssen, Roche, Celgene, IXICO, Sanofi Genzyme, Bayer Healthcare, Biologix, Genilac, Merck Serono and Teva.

**Funding**

The MS Center Amsterdam is funded by a program grant (14-358e) from the Stichting voor MS Research (Voorschoten, The Netherlands). None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Author contributions**

Conceptualization and design of the study: NLF, ID, MPW. Acquisition and analysis of data: NLF, ID, MPW, BM, FB. Statistical analysis: ID, LJB. Drafting of a significant portion of the manuscript and table: all authors