MAGNON Project: Implementation and Contribution of Lublin Criteria and quantitative MRI-Analysis for daily clinical routine of MS Patients

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Disclosures

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Introduction

- In clinical routine, there are no standardized and well-established approaches for classification of disease activity and early detection of disease progression.
- Revised Lublin criteria provide a definition of relapsing and progressive Multiple Sclerosis to classify disease activity of patients with Relapsing Remitting (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS). However, Lublin criteria are only rarely applied in clinical practice.
- Similarly, quantitative and standardized MRI analyses are not regularly used in clinical routine yet.
- **MAGNON aims to evaluate if standardized quantification of MRI data and assessment of MS patients based on the Lublin criteria provide benefits to neurologists in day-to-day management of MS patients.**
- The following interim analysis results focus on the quantification of MRI data and the putative benefit of quantitative MRI reports for neurologists.

MRI=Magnetic resonance imaging , MS=Multiple Sclerosis, RRMS= Relapsing Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis

Methods

- Until data cut-off, 583 MS patients at 54 sites in Germany were enrolled in this prospective data collection project
- Patients with early RRMS (max. 3 years since diagnosis), RRMS with suspected SPMS or SPMS according to the treating physicians' evaluation were eligible to particiate
- Project setup:
  - Per patient, two MRI scans (baseline and 12-month follow-up) are performed as part of clinical routine
  - MRI scans are analyzed using a centralized automatic processing pipeline (Biometrica MS®, jung diagnostics GmbH), and quantitative reports are provided to neurologists including information on
    - new/enlarging T2 lesions, brain and thalamic volume and volume loss per year
  - Neurologists complete questionnaires before and after receiving quantitative MRI reports

Documentation of:				
1. Clinical disease activity	X	X	X	X
2. MS subtype according to Lublin criteria	X	X	X	X
3. Value of quantitative MRI report		X		X

MRI=Magnetic resonance imaging, MS=Multiple Sclerosis

Demographics and baseline information

Focus on RRMS patients with suspected SPMS

- 583 MS patients classified as early RRMS, RRMS with suspected SPMS or SPMS were enrolled in the project at the time of data cut-off
- The majority of participants were categorized as RRMS patients with suspected SPMS
- In this subgroup ,
  - time since first suspecting SPMS ranged between 0 and 10 years with a mean of 1.5 years
  - the last relapse occurred 0-19 years ago (on average 3.3 years)

Table 1: Demographics and baseline characteristics

Variable*	Early RRMS**	RRMS with suspected SPMS	SPMS
N	34	367	182
Age, years	36.1 [20; 67]	47.3 [20; 75]	55.9 [33; 77]
Sex, female, n (%)	27 (79.4)	256 (69.8)	126 (69.2)
Time since diagnosis, years	1.7 [0; 3]	13.1 [1; 63]	17.5 [1; 39]
Time since suspected SPMS, years	n.a.	1.5 [0; 10]	n.a.
EDSS	1.3 [0; 5.0]	3.0 [0; 8.0]	4.9 [1.0; 8.5]
Time since last relapse, years	1.1 [0; 3]	3.3 [0; 19]	4.6 [0; 40]

* if not indicated otherwise, data are presented as mean [min; max]
** defined as max. 3 years since diagnosis

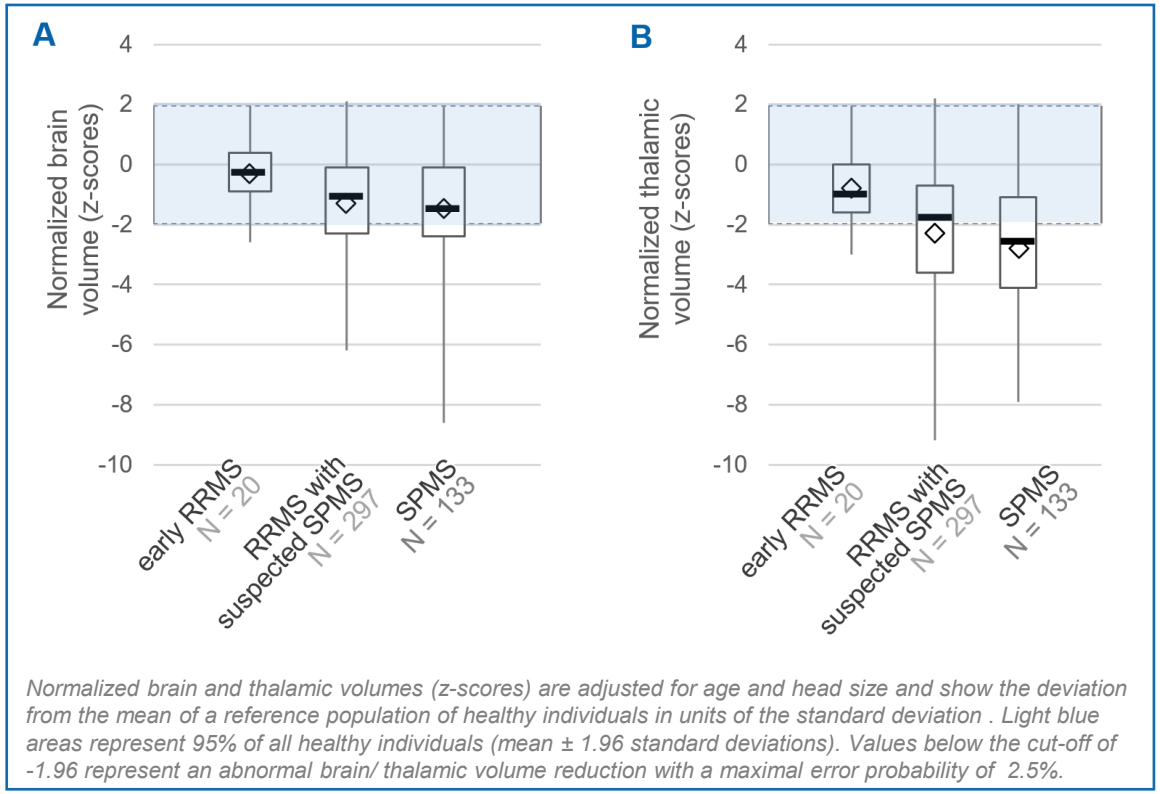
EDSS= Expanded Disability Status Scale; MS = Multiple Sclerosis

Results

Already first quantitative MRIs showed an abnormal loss of normalized thalamic volume in almost half of all RRMS patients with suspected SPMS

- In all patient groups, mean normalized brain and thalamic volumes were lower than the mean of a reference population (**Figure 1A**)
- In general, z-scores for thalamic volume were lower than for brain volume
- SPMS patients had lower z-scores than RRMS patients with suspected SPMS
- In RRMS patients with suspected SPMS, there was considerable variance of the thalamic z-score, and almost half of the patients showed age-inappropriate, reduced thalamic volume (**Figure 1B**)

Figure 1: Normalized brain and thalamic volumes



Normalized brain and thalamic volumes (z-scores) are adjusted for age and head size and show the deviation from the mean of a reference population of healthy individuals in units of the standard deviation . Light blue areas represent 95% of all healthy individuals (mean ± 1.96 standard deviations). Values below the cut-off of -1.96 represent an abnormal brain/ thalamic volume reduction with a maximal error probability of 2.5%.

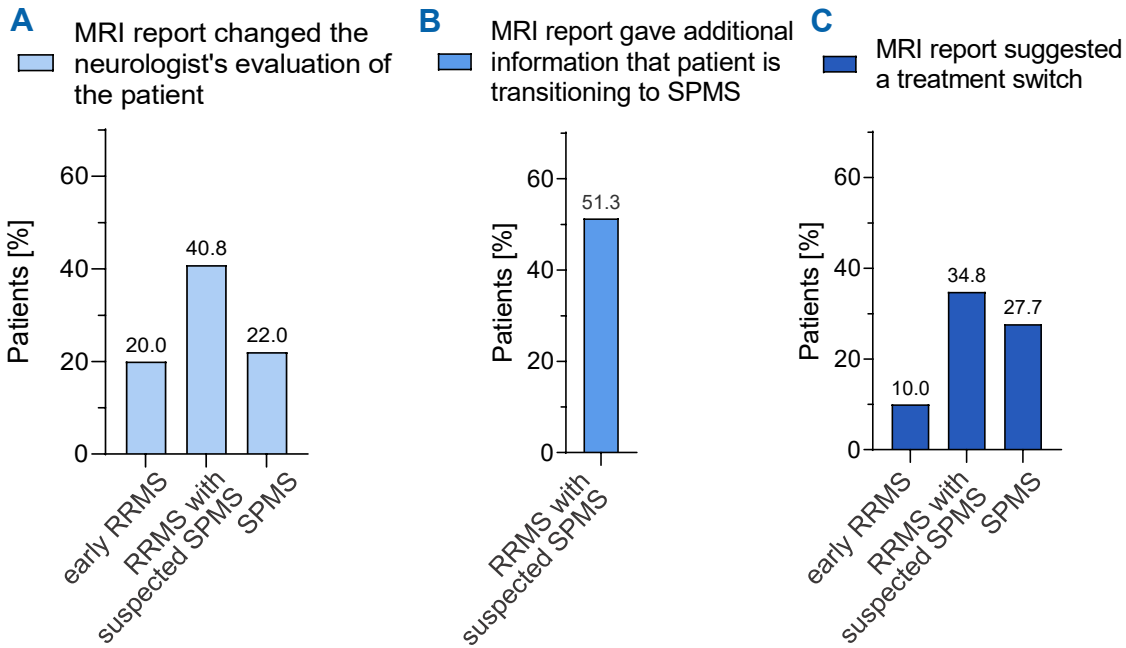
z-score = Deviation from the mean of a reference population after normalization of volume for age and head size
MRI=Magnetic resonance imaging, RRMS= Relapsing Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis

Results

Baseline quantitative MRI reports seem to be most helpful and informative for RRMS patients with suspected SPMS

- For RRMS patients with suspected SPMS , neurologists stated that the MRI report
  - changed their evaluation of the patient for 40.8%(**Figure 2A**)
  - gave additional information that patients were transitioning to SPMS in > 50% (**Figure 2B**)
  - suggested a change in therapy for 34.8% (**Figure 2C**)

Figure 2: Usefulness of single MRI reports



Graphs show the neurologists' answers documented in the questionnaire after having received the quantitative MRI report. Early RRMS (max. 3 years since diagnosis): n= 20; RRMs with suspected SPMS: n=316; SPMS: n=141

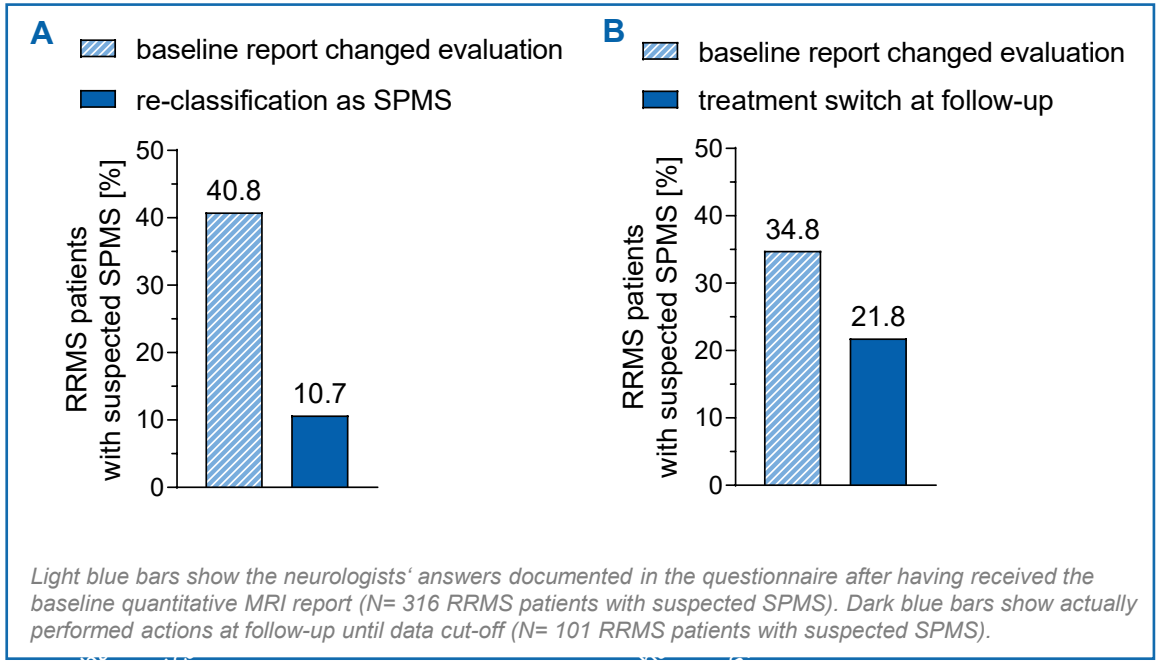
MRI=Magnetic resonance imaging, RRMS= Relapsing Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis

Results

While seen as informative, the impact of the first quantitative MRI report on clinical decisions appears to be limited

- 12 months follow-up information was available for 101 patients who were classified as RRMS with suspected SPMS at baseline. Of these,
  - 10.7% were re-classified as SPMS (**Figure 3A**)
  - 21.8% changed therapy (**Figure 3B**)
- This reflects only part of all patients in whom the neurologists interpreted the first quantitative MRI as suggesting a change in evaluation or therapy.

Figure 3: Actions taken vs. neurologist's interpretation of the first quantitative MRI report



Light blue bars show the neurologists' answers documented in the questionnaire after having received the baseline quantitative MRI report (N= 316 RRMS patients with suspected SPMS). Dark blue bars show actually performed actions at follow-up until data cut-off (N= 101 RRMS patients with suspected SPMS).

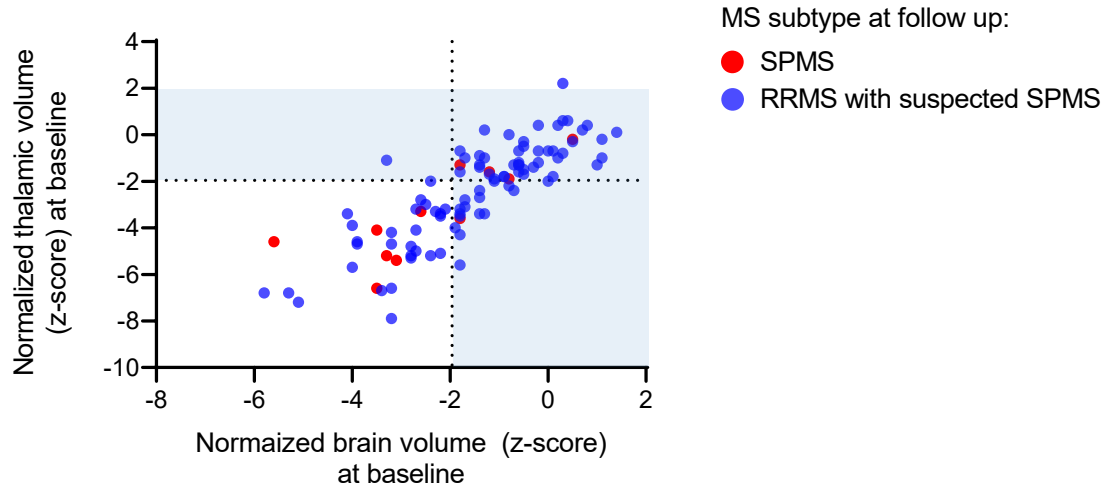
MRI=Magnetic resonance imaging, RRMS= Relapsing Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis

Results

Despite information from quantitative MRI reports, SPMS diagnosis was still reserved for older patients with a longer disease history

- Most patients who were re-classified as SPMS patients at follow-up showed abnormal brain and thalamic volume loss **(Figure 4)**
- Compared to patients who remained classified as RRMS with suspected SPMS, newly diagnosed SPMS patients tended to
  - be older
    (53.1 [44;62] years vs. 47.5 [28;70] years)
  - have a rather longer time since diagnosis
    (14.9 [5;30] years vs. 13.7 [1;63] years)
  - have been suspected to suffer from SPMS for longer
    (2.4 [0.5;7] years vs. 1.3 [0;10] years)

Figure 4: Normalized brain and thalamic volumes of RRMS patients with suspected SPMS at baseline



Normalized brain and thalamic volumes (z-scores) are adjusted for age and head size and show the deviation from the mean of a reference population of healthy individuals in units of the standard deviation. Light blue areas represent 95% of all healthy individuals (mean ± 1.96 standard deviations). Values in the lower left quater (below the cut-off of -1.96 shown by the dotted line) represent an abnormal brain and thalamic volume reduction. Shown are all RRMS patients with suspected SPMS at baseline for who follow-up data was available at the time of data cut-off (N=99)

RRMS= Relapsing Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis
Data is represented as mean [min;max]

Conclusions

- Abnormal loss of normalized brain and thalamic volume were present in almost half of all RRMS patients with suspected SPMS.
  - Abnormal thalamic volume loss indicates a higher risk of progression[1] and suggests that patients may already have transitioned to SPMS[2].
- According to neurologists, quantitative MRI reports provided additional information on patients' disease activity and disease state and informed treatment decisions, especially for RRMS patients with suspected SPMS.
- Actual changes in classification or treatment were reported only in a minority of RRMS patients with suspected SPMS .

- Final results of MAGNON will be reported in 2023, including
  - evolution of quantitative MRI parameters and Lublin criteria assessments in different MS subtypes
  - correlation of MRI results (especially brain and thalamic volume loss per year) with clinical parameters
  - predictors of disease progression

1. Hänninen et al (2019), Front Neurol ; 2. Raji et al. (2018), Front Neurol