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ORIGINAL RESEARCH ARTICLE

Neuropsychological and magnetic resonance imaging (MRI) diagnostics in secondary progressive multiple sclerosis

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ABSTRACT

Background: Multiple sclerosis is often a longitudinal disease continuum with an initial relapsing-remitting phase (RRMS) and later secondary progression (SPMS). Most currently approved therapies are not sufficiently effective in SPMS. Early detection of SPMS conversion is therefore critical for therapy selection. Important decision-making tools may include testing of partial cognitive performance and magnetic resonance imaging (MRI). **Aim of the work:** To demonstrate the importance of cognitive testing and MRI for the prediction and detection of SPMS conversion. Elaboration of strategies for follow-up and therapy management in practice, especially in outpatient care. **Material and methods:** Review based on an unsystematic literature search. **Results:** Standardized cognitive testing can be helpful for early SPMS diagnosis and facilitate progression assessment. Annual use of sensitive screening tests such as Symbol Digit Modalities Test (SDMT) and Brief Visual Memory Test-Revised (BVMT-R) or the Brief International Cognitive Assessment for MS (BICAMS) test battery is recommended. Persistent inflammatory activity on MRI in the first three years of disease and the presence of cortical lesions are predictive of SPMS conversion. Standardized MRI monitoring for features of progressive MS can support clinically and neurocognitively based suspicion of SPMS. **Discussion:** Interdisciplinary care of MS patients by clinically skilled neurologists, supported by neuropsychological testing and MRI, has a high value for SPMS prediction and diagnosis. The latter allows early conversion to appropriate therapies, as SPMS requires different interventions than RRMS. After drug switching, clinical, neuropsychological, and imaging vigilance allows stringent monitoring for neuroinflammatory and degenerative activity as well as treatment complications.

Keywords: Secondary Progressive Multiple Sclerosis; Cognition; Imaging; Magnetic Resonance Mography; Clinical Diagnosis

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1. Introduction

The central risk of multiple sclerosis is the gradual increase of irreversible functional deficits in the course of the disease. An initial relapsing course with a late transition to secondary progression is typical of the disease. Until now, the phase of secondary progression could hardly be influenced therapeutically. In the meantime, however, the therapeutic landscape has changed. Prediction of disease progression and early (and valid) detection of SPMS conversion are therefore becoming increasingly important. Cognitive and brain structural changes can play an important role in the assessment of the course of the disease.

2. Definition and pathogenesis of SPMS

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS) with a very broad spectrum of clinical and imaging findings[1]. During its course, classic MS presents as a disease continuum in which an initial relapsing-remitting MS (RRMS) very often develops into a secondary progressive form (SPMS). Clinical features of SPMS are relapse-independent progression, with or without relapses, and the absence of complete remission. In accordance with guidelines, it is characterized by a relapse-independent steady increase in clinical symptoms and neurological impairment over at least six months[2]. A distinction is made between active and inactive SPMS based on disease activity in the form of superimposed clinical relapses or inflammatory activity in magnetic resonance imaging (MRI) of the brain or spinal cord[3,4]. The relevance of difference between RRMS and SPMS as a basis for potential treatment decisions has increased with the approval of siponimod for the treatment of active SPMS in January 2020.

The mechanisms underlying the insidious progression of SPMS are incompletely understood (**Figure 1**). It is currently assumed that due to a peripherally induced and driven inflammatory process, auto-aggressive lymphocytes enter the CNS via the damaged blood-brain barrier. In addition, inflammatory foci within the CNS occur independently of the peripheral inflammatory processes when the blood-brain barrier is closed[5,6]. They appear to play a major role in the insidious disease progression[7,8]. These processes may be relevant early in the course of the disease, but they are often not detected because the resulting micro-structural damage can only be detected early with quantitative MRI methods[8-12]. In the course of the disease, the CNS intrinsic processes come to the fore and a shift from a neuroinflammatory to a neurodegenerative disease can be observed[8,13].

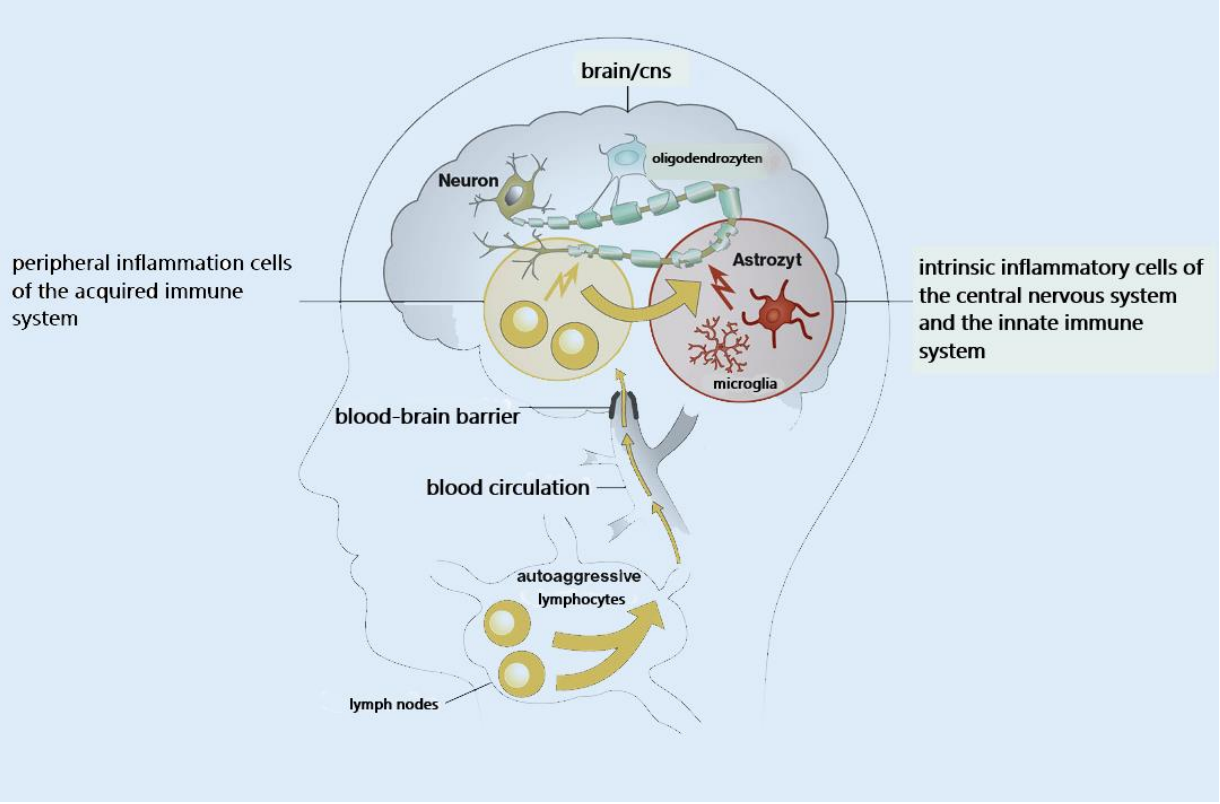

Figure 1. Peripherally induced and CNS-intrinsic inflammatory processes. (© Novartis Pharma GmbH, with kind permission).

Disability progression is a consequence of incomplete recovery of neurological functions, which reflects chronic and irreversible demyelination, axonal loss and reactive gliosis[3]. Incomplete recovery can also be explained by depleted plasticity reserves of the brain, which still compensate for the damage to the brain substance at the beginning. However, once these reserves are depleted, sensory,

motor, autonomic and cognitive abilities would be lost[14].

3. Clinical diagnosis and therapy management of SPMS in practice

During the transition to SPMS, relapses still occur initially, but then usually become less frequent[15]. Due to the overlapping relapses, early progression independent of relapse activity (PIRA) is often not recognized. A longitudinal cohort study over eight years showed a latency between first suspicion and confirmed diagnosis of SPMS of three years[16]. On the one hand, this seems to be related to the subtlety of early progression. On the other hand, in some cases, due to a lack of alternatives, the existing therapy, in particular with the βa-interferons1band1as.c., which have been approved for a long time for active SPMS (with relapses), was continued until the late stage of the disease, in which PIRA usually dominates. This may explain why the clinical data available to date have not been able to demonstrate a positive long-term effect of β-interferons on disability progression in SPMS. Until recently, treatment alternatives were only mitoxantrone, which is approved for high-activity SPMS with disability progression, thus providing an indication for selected cases with active SPMS, as well as intensified symptomatic treatment or, in case of a positive response, regular cortisone applications (intravenous or intrathecal). With a substance from the spectrum of S1P modulators (Siponimod), there is now for the first time an oral therapy approved for active SPMS, whereby "active" is defined by imposed shear and/or MRI activity[17]. This broadens the therapeutic spectrum and applications for SPMS. A significant positive effect on disability progression over two years could be documented in an SPMS population with relatively high baseline EDSS, amplified when relapse activity was still present[18]. Whether this effect is confirmed in the longer term, however, remains to be seen. In any case, these data make it clear that early and reliable detection of SPMS conversion is more important than ever as the basis for a decision on therapy. However, the unambiguous clinical definition of early SPMS remains a major challenge[19]. In addition to the clinical neurological appearance, neurocognitive testing and MRI imaging can play an important role[20,21].

4. Cognition in SPMS

Cognitive deficits have a strong negative impact on the quality of life and work ability of MS patients[22]. Deterioration in cognitive abilities is predictive of decline and loss of occupational status[23]. Thus, 34% of patients suffering from MS report a negative impact on work productivity[24]. MS patients who are not able to work also show greater cognitive impairment than those who are able to work[25]. The timing and extent of the onset of cognitive deficits are highly individual. They occur independently of the degree of disability and can appear early in the course of the disease[24].

In the stage of secondary progression, cognitive deficits are observed much more frequently. They affect approximately 40% of RRMS patients, but in SPMS the proportion increases to over 80%[26]. The high prevalence in SPMS was confirmed in a large multi-center study with a rate of 79.4%[27]. According to another study, SPMS patients not only suffer from cognitive deficits about twice as often as late-stage RRMS patients, but also more frequently than PPMS patients[28]. All of the studies mentioned also show that the profile of cognitive impairment among RRMS, SPMS, and PPMS does not differ qualitatively, and thus not primarily domain-specifically, but primarily quantitatively. Cognitive processing speed is the most vulnerable domain, the disturbance of that manifests as cognitive slowing. Despite these data, cognition has so far been rather neglected in routine diagnostics, and profiles that are dependent on the course of the disease have rarely been identified.

Indicators of cognitive deficits in practice are mainly cognitive slowing, disturbances of visual-spatial and language-related short-term memory, attentional deficits, and executive dysfunction[29]. Factors such as older age, impaired concentration, fatigue, job conflicts[24,27,30], and specific MRI changes should sensitize to cognitive deficits (see "Relationship of MRI and Cognition").

Test	Captured Domains	short description	time expenditure	frequency	BICAMS-Drums	basic testing	Minimal testing
SDMT	information processing speed	Nine pairs of numbers and symbols are shown on the test sheet. The patients have to match the corresponding number to a symbol and name it out loud. The number of correct answers in 90 seconds is measured.	approx. 3 min	once a year	+	+	+
BVMT-R	Visual-spatial short-term memory and learning	In three consecutive rounds, the patient is shown a test sheet with six geometric figures for ten seconds each. The patients are then asked to draw the figures precisely in form and position from memory on a blank sheet of paper	approx. 7min	once a year	+	+	/
VLMT	Verbal short-term memory and learning	The test material consists of a word list with 15 semantically independent words. This is read to the patient five times. After each reading, as many words as possible should be recalled directly and reproduced orally.	approx. 10min	once a year	+	/	/

recommended recommended only to a limited extent

Figure 2. Cognitive testing in practice. SDMT Symbol Digit Modalities Test, BVMT-R Brief Visual Memory Test Revised, VLMT verbal learning and memory test. (© Novartis Pharma GmbH, with kind permission).

In order to detect changes in cognitive performance in good time, cognition testing is recommended at the time of diagnosis and then annually, irrespective of the stage of the disease. Confounding effects of fatigue, depression and anxiety should be taken into account.

Cognitive performance can be assessed sufficiently well and reliably in private practice by the combined use of SDMT and BVMT-R or the use of the BICAMS test battery with SDMT, BVMT-R and VLMT (**Figure 2**). If this cannot be integrated into everyday practice, the SDMT can also be used singly. For more reliable indications of the RRMS/SPMS transition phase, however, the com bination is recommended, since SPMS patients are characterized not only by cognitive slowing but also by a decrease in visual memory performance[31]. More extensive test batteries require special centers and/or specialists such as (neuro) psychologists.

Regular and standardized testing reveals a change in cognitive domains at the individual level. Progressive MS patients perform worse in many cognitive domains than patients with relapsing-remitting MS[32]. The largest differences between RRMS and SPMS patients are in cognitive processing speed and in visual-spatial short-term

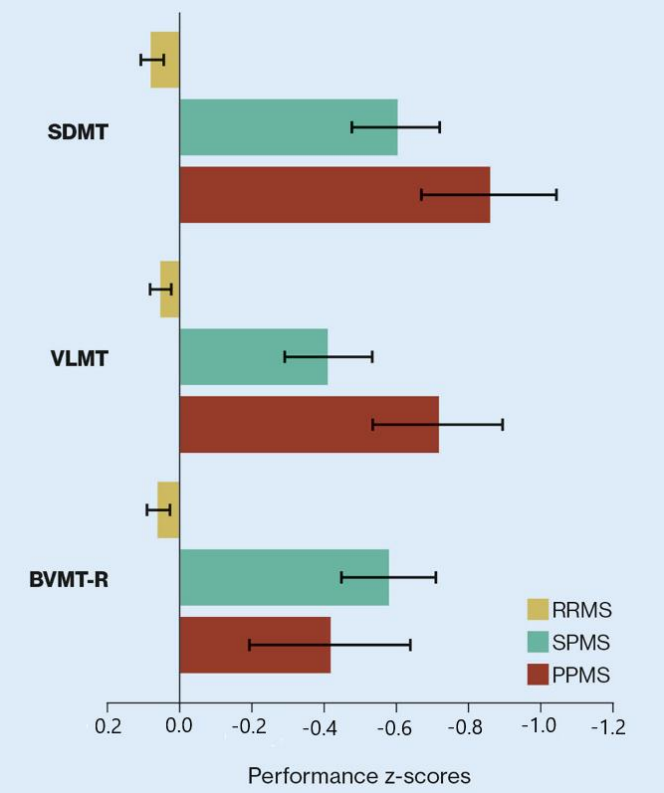

Figure 3. Results of the BICAMS test battery depending on the MS subtype (z-transformed performance scores, shown as mean and standard error). SDMT Symbol Digit Modalities Test, BVMT-R Brief Visual Memory Test Revised, VLMT verbal learning and memory test. (According to Renner *et al.*[31]).

memory and learning[32]. Visual-spatial short-term memory was also shown to be the best discriminating factor to PPMS patients (**Figure 3**).

5. Imaging in SPMS

Standardization of image acquisition and interpretation is a prerequisite for monitoring MS patients. Protocols for cerebral and spinal MRI are internationally established (**Figure 4**)[33,34].

In addition to early MRI markers for predicting long-term disability, other markers have been identified as predictive of secondary progression, such as persistent inflammatory activity in the first three years and infratentorial, spinal, and cortical lesions[35-38].

SPMS is phenotypically different from early RRMS. There is an acceleration of lesion load in the (cortical) gray matter and spinal cord, neurodegenerative progression of brain and spinal cord atrophy, and microstructural changes[39-41]. SPMS patients show a plateau in the correlation of lesion burden in the white matter in relation to physical disability[42].

Inflammatory lesions, especially barrier-disrupted lesions, are less common. Active (new or size-progressive) T2 lesions as inflammatory markers are difficult to identificate because of the frequently preexisting high lesion load. MR subtraction techniques can increase sensitivity[43]. The sensitivity of detection of cortical lesions can be increased by higher magnetic field strengths and special pulse sequences (e.g., “double inversion recovery,” “phase-sensitive inversion recovery”)[44-46]. However, a high interrater variability in the absence of standardization of the findings prevents their implementation in clinical routine[47]. The prognostic relevance and progression of spinal cord pathogy in the course of disease suggests the follow-up of asymptomatic spinal cord lesions, especially in SPMS patients[48]. Routine use of spinal MRI is feasible but requires a high level of standardization and expertise.

New inflammatory MRI markers have been suggested. Leptomeningeal B-cell follicles have been described, particularly in SPMS, as enhancement on contrast-enhanced 3D FLAIR sequences[49,50]. However, these changes seem to be constant over several years and are therefore unsuitable as progression markers[51,52]. So-called

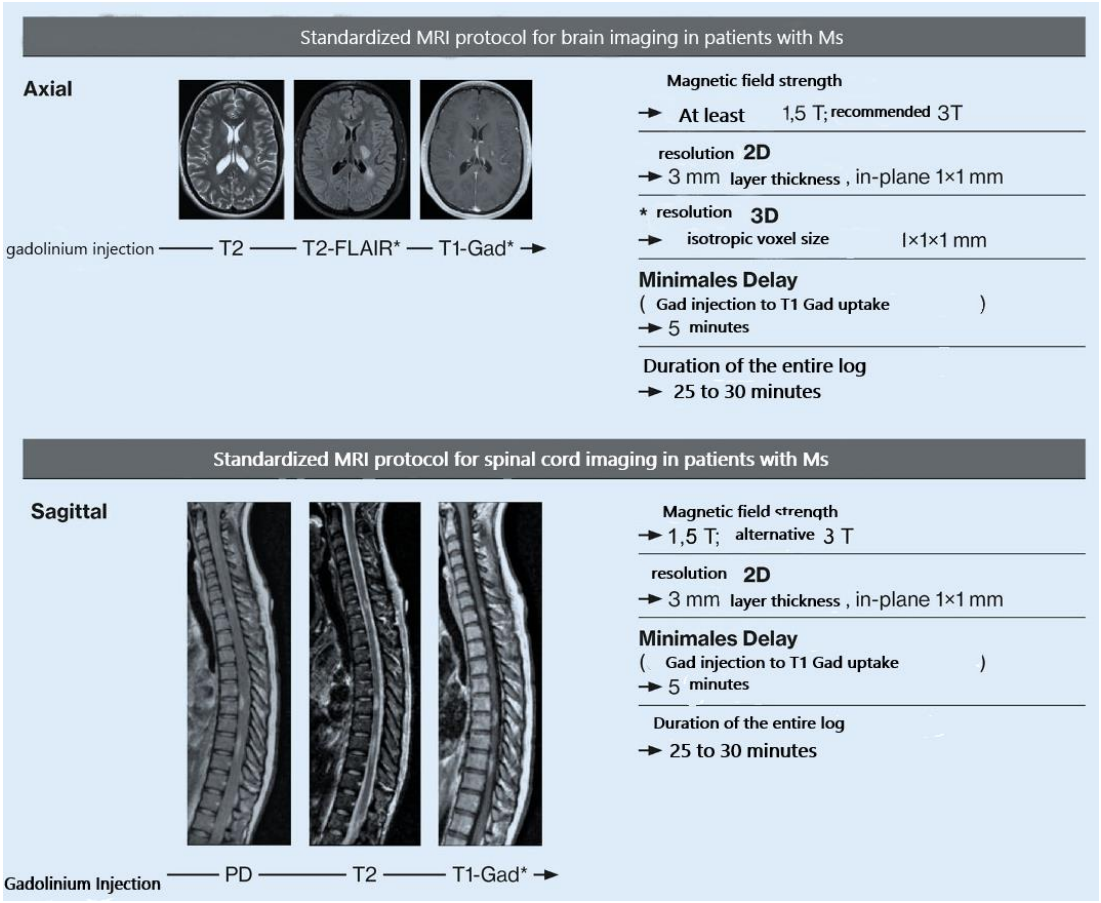

Figure 4. Internationally etablized MRI protocols in MS patients. (©M.P.Wattjes, Hannover).

chronically progressive "smoldering" (slowly expanding/evolving) MS lesions with a hypointen rim on T2* or SWI sequences have been described as characteristic in SPMS and PPMS[53,54]. Due to the slow progredience and the necessary stringent standardization of image acquisition (especially repositioning, selection of pulse sequences), routine use of this marker is questionable.

Brain and spinal cord atrophy are particularly relevant for predicting disease progression, especially cognitive deficits. The routine collection of volumetric data requires, in addition to a stringent standardization of image acquisition, the inclusion of multiple potential influences (e.g., aging, alcohol, etc.) in interpretation and subsequent therapy decisions. Therefore, brain and spinal cord atrophy is not currently recommended as a marker of individual progression in routine clinical practice[34,55], and this is not expected to change in the coming years. However, the clinical need for implementation in vigilance, especially in SPMS patients, is offensible.

Comorbidities are an important factor for individual clinical symptoms and outcome. In particular, vascular comorbidity is more frequent and more prominent in MS patients, especially in the late stages, than in healthy individuals[56]. The so-called "central vein sign" in MRI of the brain can distinguish vascular comorbidity from MS pathology. Vascular lesions usually do not show a central vein due to the lack of a perivascular distribution pattern[57]. Because vascular lesions can mimic inflammatory activity, the distinction is relevant to avoid unnecessary treatment decisions.

6. Relationship between MRI and cognition

The relevance of MRI is highlighted by the correlates of imaging and cognition. MRI correlates of cognitive dysfunction include T2-lesion load, cortical lesion load, and cortical thickness, as well as global and focal brain atrophy[58-60]. Certain lesion localization confer a higher risk for cognitive deficits. Also, which cognitive domain is impaired is partly determined by the lesion localization or distribution pattern. Lesions in the white matter are

significantly responsible for cognitive processing speed, while lesions in the deep gray matter (e.g., in the hippocampus) are frequently associated with memory deficits[60].

The interaction of white and gray matter damage leads to network collapse with marked cognitive impairment[61]. Early thalamus atrophy is particularly significant[62] and limits communication to the cortex. The majority of lesions are located in the thalamocortical connecting pathways, which disrupts connectivity subcortically to cortically and can lead to thalamic atrophy[63]. The extent of damage does not determine the extent of cognitive dysfunction, as brain plasticity and cognitive reserve first compensate for the loss of function. When these are exhausted, network collapse occurs with clinical impairments (**Figure 5**). However, since the structural damage occurs much earlier, early therapeutic intervention is important[64].

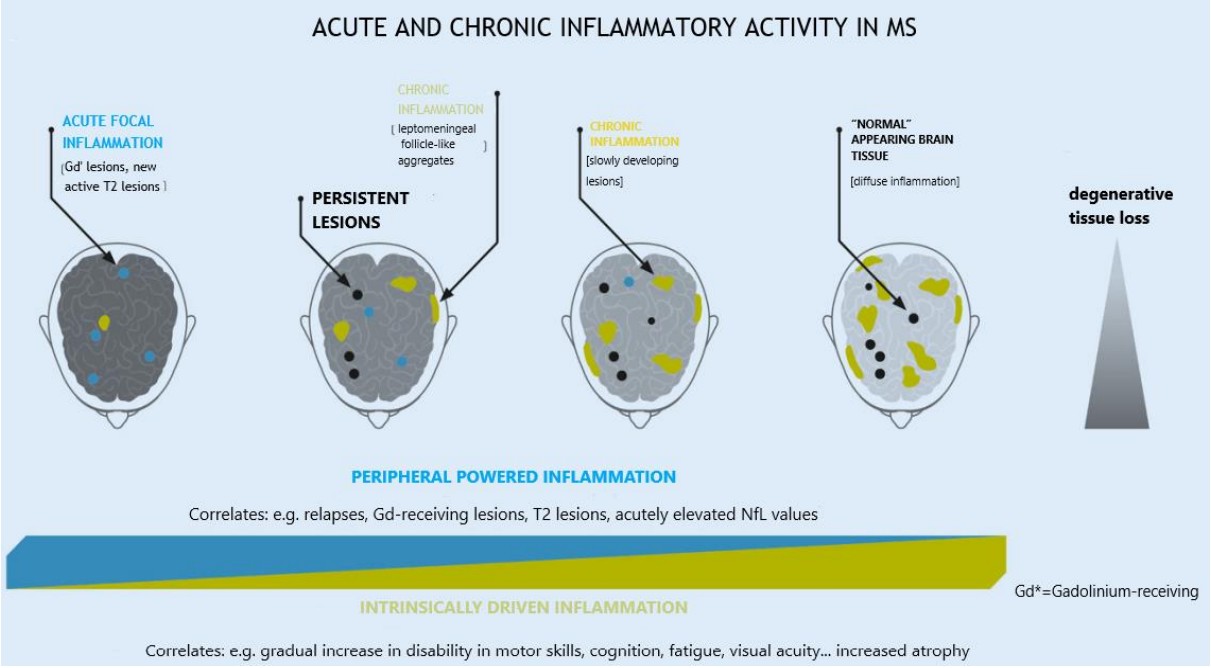

Figure 5. Inflammatory activity and accumulation of neuronal damage during the course of MS disease. (© Novartis Pharma GmbH, with kind permission).

Patients with SPMS with a smaller volume of the whole brain, thalamus and gray matter have a worse prognosis with regard to their cognitive performance. Evaluations of SDMT over 24 months as a function of brain volume show significant deterioration in patients with more atrophy. Low baseline volume of cortical gray matter, thalamus, and whole brain is significantly associated with a decline in cognitive processing speed[65]. The pathological burden in imaging suggests a higher vulnerability of the system in the future. Therefore, early effective treatment of inflammatory processes is important to minimize cognitive impairments. Patients with cognitive dysfunction at MS diagnosis show faster disability progression and more frequent SPMS conversion than patients without. Accordingly, early cognitive impairment is a predictor of long-term development[66].

Data on siponimod, also approved in 2020 for the treatment of adult patients with active SPMS, underscores the importance of early therapeutic intervention in progressive MS. Thus, the risk of EDSS progression confirmed after three and six months was statistically significantly reduced by 21% and 26%, respectively, in the entire SPMS population, and by as much as 31% and 37%, respectively, in active SPMS with superimposed relapses and/or MRI activity[18,67]. Furthermore, complementary positive results were shown in MRI endpoints for inflammatory disease activity (Gd-enhancing T1 lesions, active T2 lesions) and irreversible neurodegenerative volume loss (cortical gray substance, thalamus, and whole brain). Regarding information processing speed measured by SDMT, the risk of clinically relevant deterioration was significantly reduced by 25% in the verum group vs placebo[68].

A deterioration of 4 or more points was defined as clinically relevant, which is equivalent to a restriction of the ability to work.

7. Conclusion

The importance of detecting MS progression as early as possible has grown significantly against the background of the approval of effective new therapies. This could potentially preserve plasticity reserves in the long term and minimize functional deficits. This applies both to relapsing progressive courses and to conversion to SPMS, in which relapse-independent progression (PIRA) predominates.

In clinical practice, a temporally optimized progression diagnosis is necessary in the first step. This can be achieved by systematically examining cognitive functions in addition to symptom history and molecular parameters such as walking distance and EDSS. Furthermore, a standardized MRI examination according to the latest in ternational consensus guidelines enables the best possible assessment of progression and thus opens up possibilities for a better understanding of the individual impairment profile. For cognitive testing, annual surveys with SDMT and BVMT-R or the total BICAMS test battery are appropriate in each case. With regard to imaging, annual assessment of inflammatory activity in the CNS by means of Gd-enriched T1 lesions and active T2 lesions remains the minimum standard, even in cases where MS has been diagnosed for some time. In addition to the individual patient perspective, the aforementioned parameters can be used in individual cases to assess the course of the disease with regard to the success of the therapy.

7.1 Conclusion for practice

Early recognition of MS progression in general and SPMS conversion in particular and targeted therapeutic intervention are important to prevent functional deficits in the long term.

An annual cognitive test using SDMT and BVMT-R or BICAMS provides relevant information for diagnosis and assessment.

Once-yearly MRI imaging of Gd-enhancing T1 lesions and active T2 lesions is also relevant in SPMS. New MRI markers are not yet available in clinical routine. Sensitization and awareness of the interplay of clinical, neuropsychological, and MRI parameters will enable better monitoring of patients in the future with respect to neuroinflammatory and neurodegenerative activity as well as potential therapeutic complications.

Conflict of interest

The authors declared no conflict of interest.

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