

REVIEW ARTICLE

Multiple sclerosis and cognitive disorders.**What should neurologists advice patient with ms about his risk of developing dementia****Daniel BARTKO¹, Igor ČOMBOR¹, Katarina KUBOVIČOVÁ², Zlatica GOMBOŠOVÁ¹**

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Abstract

This review article deals with patients suffering from multiple sclerosis associated with cognitive impairment or dementia. Cognitive decline is common in approx. 40–70% of patients with multiple sclerosis (MS). Cognitive symptoms are observed across all disease subtypes but they tend to be more significant in primary and secondary progressive MS. Although the overall prevalence of cognitive decline increases with disease duration, significant dementia develops in a variable minority. Cognitive decline is moderate but it tends to be more severe in older patients and in females. Unambiguous dementia is observed in approx. 5% of cases. For individual patients with MS and their families and friends the cognitive decline brings many problems arising from patient's life, his disability, memory loss, emotional problems, family problems, loss of working place, etc. All contribute importantly to social handicap over and above the degree of physical impairment. In this situation, it is very important what Neurologists should tell patients or their families regarding the risk of developing dementia. There exist various approaches: 1. Prevalence of cognitive decline is high but significant dementia develops only in minority of patients. 2. Cognitive decline is mostly moderate and generalized intellectual deficit is uncommon. 3. Some cognitive functions are very vulnerable, but a number of specific cognitive capacities are spared. 4. Patients with relapsing remitting MS belong to a relatively favourable prognostic group regarding the risk of dementia. All this and many other approaches are necessary to tell the patient, to inform him very precisely, to tell him, that patients with RR MS have relatively favourable prognosis, simply to give him optimistic hope, not extremely optimistic. A really optimistic approach and communication can bring the patient the hope for better life. Optimism and brain plasticity and recovery of brain functions play here very important roles.

INTRODUCTION

Cognitive dysfunction has been described since the first data about MS were noted. At the end of 19th century, memory, emotional as well as intellect impairments, were described by Charcot. At the beginning of 20th until now there have been many discussions if these symptoms are typical, characteristic or specific for SM. First of all, we have to try to define the term “*dementia*”

WHAT IS DEMENTIA?

For the problem, mentioned in the title, the precise definition of dementia is very important. Is it a specific disease, clinical entity, and/or is it a syndrome? It is not a specific disease. It is a descriptive term for a collection of symptoms that can be caused by a number of disorders affecting the brain. They are characterized by:

1. Significantly impaired intellectual functioning interfering with normal activities.
2. Loss of the ability to solve daily problems and maintain emotional control.
3. Personality and behavioral changes (*agitation, delusions, hallucinations*).
4. *Time and place* disorientation (NINDS, 2006).

Memory loss does not mean that a person suffers from dementia. Diagnosis “*dementia*” can be used ONLY if two or more brain functions are significantly impaired (*memory, language skills, perception etc*). For precise diagnosis, a full neuropsychological evaluation is needed (Benedict *et al* 2002). Currently, two tests of processing speed have been suggested for use as in-office screening tests: the PASAT and SDMT (Drake *et al* 2010).

There is another term “MILD COGNITIVE IMPAIRMENT” (MCI). What does it mean? Cognitive and memory impairment are not severe enough to be diagnosed as dementia but they are more pronounced than similar changes associated with normal aging although some patients with MCI later develop dementia (Petersen 2006). For many years, it has been well known that cognitive dysfunction in MS has a spec-

trum of severity ranging from mild task-specific deficits (MCI) to severe global cognitive decline (Chiaravalloti & DeLuca 2008). Cognitive impairment predominantly reflects involvement of subcortical pathways, with such symptoms as attention, concentration, processing speed, encoding of new information, working memory, executive functions and affect (Waren 2010).

This complex of symptoms is non-specific and it has limited diagnostic usefulness because we can find similar deficits in most ‘subcortical dementias’. It is necessary to stress that the spectrum of cognitive dysfunction in MS is much broader than can be discovered during conventional neurologic investigation. It consists of many various emotional and social aspects (Banati *et al* 2010). Only some of them are described during such examination despite many various cognitive domains which are part of MS symptomatology. In MS they showed

- High frequency.
- Wide individual variations.
- Only weak correlation with neurological deficit.

Except Cognitive dysfunction in MS we can recognize such important domains as

- decreasing quality of life (QoL),
- fatigue,
- pain,
- visual impairment,
- depression,
- impaired social functioning,
- dizziness/vertigo,
- loss of self-management capabilities,
- emotional disturbances etc.
- many of these domains are reported by patients with MS.

HOW COMMON IS COGNITIVE IMPAIRMENT IN MS?

This question is very important for Neurologists during communication regarding possibility to develop dementia. From 40 to 70% of MS patients suffer from cognitive impairment. Even people who recently started to have other MS symptoms may have cognitive dysfunction, but it might be so subtle that they did not even notice them or attribute them to other things, such as aging or being tired.

Another major domain in MS is *fatigue*. It occurs in approx. 75% of MS patients. It is one of the most disabling symptoms; one of the worst symptoms considerably limiting daily activities and communication (Table 1).

On the contrary, *classical disconnection syndromes* are rare. Despite this, the cognitive effects of MS may reflect at least disruption of cortico-subcortical networks, including ascending cholinergic and other neurotransmitter pathways (Penny *et al* 2010; Amato *et al* 2006) (Table 2).

Tab.1. Impact of cognitive impairment in MS patients (Foley & Brandes 2009).

Prevalence	Up to 70% of people with MS
Effects	Decreased information processing speed Impaired recall Diminished attention and concentration capabilities Impaired executive functions
Testing modalities	PASAT-3; MSNQ; SDMT; MSNQ

MS = multiple sclerosis; PASAT-3 = Paced Auditory Serial Addition Task; MSNQ=Multiple Sclerosis Neuropsychological Questionnaire; SDMT = Symbol Digit Modalities Test

ARE THERE CORRELATIONS BETWEEN SEVERITY OF COGNITIVE DECLINE AND AGE OF PATIENTS, DURATION OF MS, BRAIN ATROPHY AND TOTAL LESION LOAD (WHITE MATTER LESION VOLUME) AND TYPE OF MS?

1. Few literary data documented that there is correlation between severity of cognitive impairment and duration of disease.
2. But the correlation with total lesion load is less documented (Chiaravalloti & DeLuca 2008; Amato *et al* 2001; Calabrese *et al* 2009; Penny *et al* 2010).
3. Only white matter lesion volume and cortical atrophy has been shown to be the best MS predictor of overall cognitive function after five years in primary progressive MS (Penny *et al* 2010). From all these correlations it can be concluded that the relations are not simple, mainly due to general practice without a sufficient spectrum of neuropsychological examination.
4. Regarding the age, until now the effect of age was not documented which may be due to difficulties to assess it (Smestad *et al* 2010).
5. Cognitive dysfunction and type of MS. Cognitive symptoms are observed across all disease subtypes but cognitive decline tends to be more significant in primary and secondary progressive MS, probably reflecting the relative extent of white matter damage (Waren 2010). Cognitive dysfunction in MS correlates with more permanent destruction of brain tissue, such as "black holes" and atrophy. Therefore, cognitive dysfunction tends to be worse in people with progressive forms of MS than in people with relapsing-remitting MS. In general, people with progressive MS seem to be more severely affected however, as mentioned before, even people with very little disability can experience some degree of cognitive dysfunction). People with more pronounced cognitive dysfunction tend to have:
 - a. **More T1-weighted lesions:** These are also called "black holes" and indicate that there has been destruction of nerve axons, not just demyelination.
 - b. **Atrophy of corpus callosum:** This means that the bundle of nerve fibers that connect the right and left hemispheres of the brain has shrunk, due to destruction of nerve cells
 - c. **Cortical atrophy.** The role of cortical damage is increasingly recognized (Penny *et al* 2010; Calabrese *et al* 2009).

However, the patient status can also be made temporarily worse by other symptoms of MS, such as fatigue and depression, as it was mentioned above. From these data can be concluded that since cognitive deterioration can signal disease progression in the absence of

Tab.2. Impact of fatigue (Foley & Brandes 2009).

Prevalence	Up to 75% of people with MS experience fatigue on a daily basis
Effects	Negative impact on Daily activities Perception of general and mental health and QoL
Testing modalities	FSS; MFIS

MS = multiple sclerosis; QoL = quality of life; FSS = Fatigue Severity Score; MFIS = Modified Fatigue Impact Scale

increasing physical disability, there is a need for simple and reliable cognitive metrics and for incorporating them into the routine assessment of patients.

WHAT IS THE BEST ADVICE FOR THE PATIENTS WITH MS AS TO THEIR RISK OF DEVELOPMENT OF DEMENTIA? IMPLICATIONS FOR PRACTICE IN MS PATIENTS:

For individual patients with MS and their families, cognitive decline understandably brings many problems arising from patient's life, his disability, memory loss, emotional problems. All contribute importantly to social handicaps over and above the degree of physical impairment (Amato *et al* 2001).

Every Neurologist has to know:

1. How dementia is defined?
2. How frequently it occurs.
3. Correlations between cognitive deficit and MS subtypes.
4. Cognitive deficit and duration of MS.
5. Correlations between severity of MS and cognitive deficit.
6. Prevalence of severe degrees of cognitive deficit in MS.
7. Cognitive deficit in MS regarding male and female patients.
8. Dementia in MS and age.
9. Dementia in MS and MRI findings as predictors of outcome.
10. Dementia as an early and prominent symptom supervenes on longstanding stable MS.
11. Pharmacological and non-pharmacological therapeutic possibilities in MS dementia guide-lines.
12. WHAT we should advise MS patients regarding the risk of developing dementia.

We have to know the answers for all these questions and problems. If we know them, our decision as to what to advise patients regarding their MS and possible development of dementia will be easier, understandable and effective.

Ad 1. Definition of dementia. It is a descriptive term for a collection of symptoms that can be caused by number of disorders affecting the brain. They are characterized by:

1. Significantly impaired intellectual functioning interfering with normal activities.
2. Loss of the ability to solve daily problems and maintain emotional control.
3. Personality and behavioral changes (*agitation, delusions, hallucinations*).
4. Disorientation to time and place (*NINDS, 2006*).

Memory loss does not mean that a person suffers from dementia. Such fact should be told to the patient, his family, his Neurologist and his Family Doctor: but told mainly to the patient!

Ad 2, 3, 4. Frequency, subtypes, duration. Cognitive decline in MS varies depending in part on a) how it is defined and b) how it is measured, but it is common in approx. 40–70% of patients. Cognitive symptoms are observed across all disease subtypes but this decline tends to be more significant in primary and secondary progressive MS, probably reflecting the relative extent of white matter damage (Waren 2010). Although the overall prevalence of cognitive deficits increases with disease duration (Amato *et al* 2001) significant dementia develops only in a variable minority (Chiaravalloti & DeLuca 2008). During discussion with the patient tell him all these data, mainly,

1. Dementia is not a frequent symptom. Unambiguous dementia as a symptoms of MS is observed in approx. only 5% of cases (Staff *et al* 2009).
2. Dementia occurs in secondary progressive type of MS and this type is not frequent compared to RR MS.

Tell these data the patient!

Ad 5,6,7,8. Severity of MS, severity of cognitive decline, dementia early prominent symptom. Cognitive symptoms are observed across all disease subtypes, but cognitive decline tends to be more significant in primary and secondary progressive MS (Waren 2010) and when relapsing remitting MS cognitive decline is moderate. It has the tendency to be more severe in older patients and in females (Prakash *et al* 2008).

This information is one of the most important for discussion with the patient!

Dementia as an early or prominent symptom is a very interesting problem. It represents a clinical situation showing patients with significant cognitive decline which supervenes on longstanding MS that is apparently otherwise stable.

Ad 9, 10. Dementia in MS and MRI findings as a predictor of outcome. Many white matter lesions on initial MRI are a predictor of cognitive decline in the inter-

mediate to longer term but severe cognitive decline is not the major determinant of overall functional status. Conclusions from analysis of 31 trials have shown:

1. Some existing MRI findings bring little, if any ancillary value beyond relapse and disability outcome.
2. New approaches as MRS quantitative atrophy measures (MRI), DWI can add new data.
3. New data can also show MSFC scale (Multiple Sclerosis Functional Composite). It includes disease-specific psychometrically sophisticated clinical outcome measures that evaluate both cognitive and physical domains. All this can bring new hope for qualitatively better evaluation of patients with MS associated with cognitive decline.

Tell this information to the patient!

Ad 11. What should the patient be told about management options? Can cognitive decline be treated?

The answer for this question is very important if we want to advice patients and their families about the risk of development of dementia and should be included in our discussion with the patient.

Improvement in symptoms and in quality of life can be achieved with a combination of various approaches, pharmacological, non-pharmacological including neuro-rehabilitation and neuropsychological and behavioral techniques.

Potential management strategies for MS-related cognitive impairment should include pharmacologic approaches, such as disease-modifying therapy, acetylcholinesterase inhibitors, and l-amphetamine; behavioral therapies, such as cognitive rehabilitation and speech or occupational therapy; and supportive psychotherapy. The data for all these options, however, are insufficient regarding proven efficacy. Nevertheless, existing data do suggest that one or more of these options may be worth trying and can offer improvement in symptoms and quality of life.

Although the research on the effectiveness of cognitive rehabilitation in MS is in its infancy, there are some data to support a referral for such therapy. An expert review panel conducted a meta-analysis to evaluate the status of research on cognitive rehabilitation in MS and to recommend practice guidelines (O'Brien *et al* 2008). Non-interventional and non-peer-reviewed studies, as well as review or theoretical articles, case reports without empirical data, were excluded from the analysis.

From an initial list of 224 citations, 16 studies met the inclusion criteria, and most of these focused on learning and memory deficits. Unfortunately, no studies of cognitive rehabilitation in the area of processing speed had been done as of the time of this analysis.

The expert review panel recommended one practice guideline based on a 2005 randomized trial that pro-

vided data to support a memory retraining protocol (O'Brien *et al* 2008; Chiaravalloti *et al* 2005). The trial enrolled 29 subjects with MS-related learning deficits and randomized them to either the control group (n=14) or the experimental group (n=15, Chiaravalloti *et al* 2005). Both groups participated in 8 "treatment" sessions, which consisted of no training memory tasks for the control group and the Story Memory Technique (SMT), which taught the skills of visualization and context to improve learning, for the experimental group (Chiaravalloti *et al* 2005). In subjects with moderately severe impairment, 88% in the experimental group showed significant improvement in learning abilities compared with 38% in the control group ($p < 0.01$, Chiaravalloti *et al* 2005). Subjects with mild impairment showed little improvement (Chiaravalloti *et al* 2005). On this basis, the technique used in this study was recommended by the review panel as a practice guideline for the rehabilitation of learning and memory in persons with MS (O'Brien *et al* 2008).

The panel also recommended self-generation to improve verbal learning as a practice option based on two studies (O'Brien *et al* 2008; Chiaravalloti & DeLuca 2002; Basso *et al* 2006). Self-generation as a technique is founded on the concept that an individual better remembers items he or she generated compared with items he or she only read about (Chiaravalloti & DeLuca 2002).

The evidence of benefits from cognitive rehabilitation in the allied field of traumatic brain injury also supports such a referral (Cicerone *et al* 2005). The number of studies of cognitive rehabilitation in the setting of traumatic brain injury rose eight-fold, from 32 to 258, between 1999 and 2005 (O'Brien *et al* 2008). A similar research in MS is needed:

- a. Mixed data can be found on pharmacologic approaches to the treatment of cognitive impairment in MS. Only interferon beta-1a has shown positive data, with significant improvement in processing and learning/memory (Fischer *et al* 2000; Patti *et al* 2010). Initial data on donepezil showed improvement in memory (Krupp *et al* 2004) but this finding was not supported by a more recent and larger trial that showed no effect (Krupp *et al* 2010). L-amphetamine has shown promising data in two trials, although one trial lacked a placebo control (Benedict *et al* 2008) and the other, a larger randomized controlled trial, reported positive findings on a secondary, rather than primary, outcome measure. These findings need to be replicated (Morrow *et al* 2009).
- b. Fatigue and depression are common in MS, and their treatment may substantially improve overall quality of life
- c. We can conclude that there is modest evidence for a useful benefit from acetylcholinesterase inhibition (Donepezil) on learning and memory and everyday functioning (Chiaravalloti &

DeLuca 2008; Amato *et al* 2001). For present, the use of cholinesterase inhibitors for MS is not covered by NICE guidelines in the UK.

- d. Non-pharmacological cognitive rehabilitation programme in MS is similarly limited. For all pharmacological approaches, further randomized placebo-controlled trial are needed.

Finally, the very important question: What should we tell the patient or his family regarding the risk of developing dementia? The answer is not easy. There are three possibilities:

- Development of dementia is possible
- Development of dementia is not possible
- Development of dementia is possible but is rare.

If development of dementia is possible, then it is necessary to take into account:

1. Try to uncover what is behind this question.
2. What do the patient and his family understand about "dementia"?
3. Many General Practitioners, some Neurologists and – of course – patients, do not completely understand what "dementia" means.

Therefore, the patient needs more information about MS and possible risk of dementia. Cognitive decline is common in MS patients but the generalized intellectual decline ('dementia') is uncommon. How does it manifest? Typically: memory, attention and executive functions are predominantly affected.

WHAT IS THE COGNITIVE OUTLOOK FOR PATIENT?

Cognitive impairment tends to correlate with:

- a. Disease stage
- b. Overall severity and
- c. Disease progression and dementia as a predictor of outcome.
- d. Prognosis in the individual patient is difficult to presume.

Tell and/or don't tell the patient?

Executive functions (everyday memory, concentration, planning ability) are most vulnerable in MS, whereas a number of specific cognitive capacities are spared (Waren 2010). This information is very important and it is necessary to know and to tell the patient!

Another approach: The patient with relapsing-remitting MS (according to current therapeutic evidences) belongs to a relatively favorable prognostic group regarding the risk of dementia. Tell this important information the patient!

Another important aspect: Is it always MS?

The possibility of a second/another disease process should always be kept in mind. Mainly, is the cognitive

dysfunction a) dominant or b) rapidly evolving in relation to other disease indices (atypical MRI, e. g. focal atrophy)? Or, is there a strong family history of dementia?

Very precise family history is needed to be sure what tell to the patient.

GUIDELINE FOR “WHAT SHOULD WE TELL THE PATIENT?”

There is no simple answer to the question of ‘dementia risk’. We must take into account:

- a. Specific characteristics of the individual patient’s MS.
- b. Disease evolution.
- c. The background of the question (to try to uncover what is behind the question to explain what “dementia” means).
- d. Patient wants more information.

Tell the patient that cognitive symptoms are common in MS but generalized intellectual decline (‘dementia’ in the traditional sense) is uncommon.

Tell the patient this information!

- e. Despite typically everyday memory, concentration, planning ability (i.e., executive functions) are most vulnerable, a number of specific cognitive capacities are spared

Tell the patient this important information!

- f. While there is no very effective treatment for cognitive symptoms per se. There are possibilities to treat – in a certain sense – effectively the disease and by treating disease, many other – potentially treated – symptom as fatigue, spasticity, mood and others can be treated.

Explain these possibilities to the patient!

- g. It also seems appropriate to suggest to the patient that new scientific information, relevant to the question of MS, its pathophysiology, mechanisms of onset, prognosis, effective treatment and association to cognitive decline will soon be forthcoming. For these suggestions in MS, there exist many scientific proofs.

Tell this information to the patient!

- h. Precise prognosis regarding cognitive decline and dementia in the individual case is easy, however, a patient with RR MS disease which, on current evidence, has a relatively favorable prognosis. Give him this optimistic hope! Not extremely optimistic, but still an optimistic approach and communication can bring hope for a better life.

OPTIMISM AND BRAIN PLASTICITY (SCIENTIFIC THOUGHT)

Optimism is an expectation of positive results in the future. It has positive effect on our life and our health – this was documented by fMRI study. Following optimistic stimuli, it was found activation of two brain areas, amygdale and anterior rostral cinguli cortex demyelination and axonal damage reflects loss of function. Stimulation (of various origins) is followed as a basis for recovery of brain function activation by creating new neuronal pathways. It is a basis for brain plasticity, new neuronal network and synapses, and this is a basis for recovery of brain functions. The brain is the greatest miracle; therefore, it is not repetitive.

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