

## **Neuroimaging and genetic correlates of cognitive dysfunction in multiple sclerosis**

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### **Summary**

Cognitive impairment occurs in 40–70% of patients with multiple sclerosis (MS). It is observed even at the early stage of disease, including clinically isolated syndrome (CIS). Cognitive dysfunction develops irrespectively of the physical disability. Affected domains include: information processing speed, visuospatial abilities, attention, verbal memory and executive functions. Cognitive deficits have relevant implication because of their impact on daily living, quality of life and increased risk of conversion from CIS to MS. In the recent years the issue of cognitive impairment in MS became an important research problem. The fundamental aim is to understand the neurobiological substrates of these mental symptoms. As we know neurodegenerative process associated with the disease, pathology of cerebral cortex and damage to the normal appearing brain tissue are potentially involved in the development of cognitive symptoms. Better assessment of these cerebral changes is possible through the improvement of magnetic resonance imaging techniques. Influence of genetic profile on the course of MS, including cognitive dysfunction, is still under evaluation. Despite using the new neuroimaging methods, the substrate of cognitive impairment in MS has not been clearly defined so far. Understanding the mechanisms underlying cognitive symptoms may extend our knowledge of the pathophysiology of the disease and also contribute to the development of new strategies and objectives for treatment. This paper provides a summary of the results obtained from the application of conventional and modern magnetic resonance imaging techniques to assess structural pathologies occurring in MS as well as genetic factors and their association with cognitive dysfunction.

**Key words:** multiple sclerosis, cognitive function, magnetic resonance imaging

## Introduction

In the recent years the issue of cognitive impairment in multiple sclerosis (MS) became an important research problem. The fundamental aim is to understand the neurobiological substrates of these mental symptoms in patients suffering from MS. Some factors, which may allow selecting a group of patients at increased risk of cognitive impairment, are sought.

Cognitive dysfunction occurs in 40–70% of patients in the course of MS [1, 2]. It has significant influence on the quality of life caused by increased unemployment rate, restriction of social activities and interpersonal relationships, sexual dysfunction and difficulties in performing routine household tasks [3]. Sartori and Edan determined that the unemployment rate among individuals suffering from MS who were cognitively impaired was 79% compared to 27% among patients without cognitive dysfunction [4].

Clinically isolated syndrome (CIS) is an individual's first episode of neurological symptoms, lasting at least 24 hours, caused by demyelination. The risk of conversion from CIS to MS mainly depends on the presence of demyelinating lesions in the central nervous system detected by magnetic resonance imaging (MRI). In case of individuals with MRI lesions the risk of conversion is from 60 to 80%, while absence of MRI lesions is associated with approximately 20% risk for developing MS [5]. Cognitive impairment occurs in 18–57% of patients after CIS [6–9]. Postulated causes of such discrepancies are: usage of diverse batteries of neuropsychological tests, different reference values for tests and various criteria used to distinguish between cognitively preserved and impaired individuals. Occurrence of cognitive dysfunction after CIS is clinically significant not only through the impact on quality of life, it is also important because of association with the increased risk of conversion from CIS to MS [9, 10]. Thus it turned out that the process of cognitive deterioration may start from the early stage of MS. An additional evidence for the early development of cognitive symptoms in case of some individuals is provided by the research on a group of patients with radiologically isolated syndrome (RIS). It is a recently defined entity characterized by the presence of lesions suggestive of MS on brain MRI images without neurological symptoms expression and with a normal neurological examination [11]. This stage of disease is apparently asymptomatic, however, in case of some patients cognitive impairment was demonstrated [12].

Neuropsychological examination essentially extends the overall assessment of a patient suffering from MS. Presence of cognitive impairment and its progression should be considered as a marker of disease progression and an important factor determining the early initiation of disease-modifying therapy after CIS. This is particularly important in the context of clinical trials which indicate that early initiation of treatment is beneficial for patients [13]. Moreover, significant impact of this therapy on cognitive function was proved [14].

### **Profile and substrate of cognitive impairment in MS**

The profile of cognitive dysfunction in MS and CIS is similar. Negative impact on various aspects of cognitive processes was observed, however, mostly affected domains include: information processing speed, visuospatial perception, attention, verbal memory and executive functioning [6, 8, 9, 15–18]. The most commonly used neuropsychological tests assessing cognitive functioning in MS and CIS include: SDMT (Symbol Digit Modalities Test) – the most sensitive test for cognitive dysfunction in MS [19], PASAT (Paced Auditory Serial Attention Test), TMT (Trail Making Test), verbal fluency tests, WCST (Wisconsin Card Sorting Test), SRT (Selective Reminding Test) and SPART (10/36 Spatial Recall Test). ‘Brief Repeatable Battery of Neuropsychological Tests’ (BRB-N) is a frequently used set of neuropsychological tests used to assess cognitive function in MS. It contains: Selective Reminding Test, 10/36 Spatial Recall Test, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test and Word List Generation [20, 21].

The substrate of cognitive impairment in MS has not been clarified so far. Many studies were conducted to find some factors associated with the occurrence of cognitive dysfunction. It was determined that the risk factors for cognitive deterioration are: male sex, early onset of disease, secondary progressive course and low premorbid cognitive status [22]. Correlation between neurological status (scored in EDSS) and cognition was proved to be low [23, 24]. It follows that cognitive impairment develops irrespectively of physical disability. Moreover, there are reported cases of MS characterized by predominant or exclusive cognitive symptoms (cog-MS) [25].

In case of patients in the early stage of MS, including individuals after CIS, there was found no correlation between cognitive functioning and neurological status scored in EDSS [6, 7, 26]. It was shown that the course of cognitive disorders in MS is progressive. Individuals presenting dysfunction at the early stage deteriorate later, while cognitive status in case of patients cognitively preserved does not change over time [27].

### **Correlations between cognitive function, demyelinating lesions and atrophy assessed with MRI**

MRI provides many findings related to the substrate of cognitive impairment in MS. Two pathophysiological components of MS can be assessed with support of the MRI scans – inflammatory activity and neurodegeneration. Correlates of the first component are demyelinating lesions occurring as hyperintense on T2-weighted images and isointense or hypointense on T1-weighted images. Neurodegenerative component is reflected primarily by atrophy of the brain tissue.

It was determined in the studies that correlation between T2 hyperintense lesions (taking into account number of lesions and total lesion volume) and the occurrence of cognitive dysfunction is modest at best [28–30]. In addition, correlation between total lesion volume and severity of cognitive deterioration was not observed [31]. Presence of gadolinium enhancing lesions did not affect cognitive function in MS patients [28, 32]. However, it was noticed in another study that patients during relapse (optic nerves

and motor function of upper extremities were not involved), among which 93% had active lesions, performed significantly worse in SDMT than before and 3 months after relapse [33]. Moreover, study showed that active lesions are common (72%) in MS patients with a pure cognitive onset, which subsequently remains the predominant manifestation (cog-MS) – this relation requires further evaluation [34].

In contrast to neurological deficits in MS, cognitive impairment is not associated with specific focal lesions, it rather reflects global structural and functional disorder of the brain. However, some studies proved the association between changes in certain brain structures with a specific pattern of cognitive deficits, for instance location of lesions in the frontal area affected executive functioning, solving problems, verbal memory and verbal fluency, while lesions occurring in left parieto-occipital area were correlated with visuospatial skills and verbal memory impairment [35, 36]. Another research did not indicate any association between cognitive dysfunctions and location of lesions [32].

Besides demyelinating process, neurodegeneration is an important aspect of the pathophysiology of MS. Degeneration markers, such as brain atrophy, are significantly associated with the cognitive deterioration in MS patients [28, 30, 37, 38]. Such correlations were also shown for the assessment of regional atrophy, for instance gray matter atrophy. The studies provided many evidences for the involvement of the cerebral cortex in MS. The occurrence of lesions located in the gray matter was confirmed [39]. The association between cognitive functioning and the number and volume of these cortical lesions was also determined [28, 40, 41]. Moreover, cerebral cortex atrophy is an important factor differentiating between cognitively impaired and cognitively preserved individuals [7, 28, 42–44].

Atrophy of other brain structures is also associated with cognitive deterioration in MS patients. It applies to the corpus callosum and hippocampus [45, 46]. In case of corpus callosum, impact of lesions location was also shown – anterior region atrophy affected memory impairment, while posterior region atrophy was related to information processing speed [45]. Atrophy of the central nervous system, especially diencephalon, is reflected in the width of the third ventricle, which turned out to be another parameter correlated with cognitive efficiency [44, 47].

### **Impact of damage to the normal appearing brain tissue on cognitive dysfunction**

Normal appearing brain tissue (NABT) is the area of brain presenting no abnormalities in standard MRI images. It is possible to detect a damage to NABT through the use of more sensitive neuroimaging techniques such as diffusion tensor imaging (DTI), magnetization transfer imaging (MTI) and proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS). NABT consists of normal appearing white matter (NAWM) and normal appearing grey matter (NAGM).

It appears that abnormalities in the area of NABT are significant factors determining cognitive dysfunction in MS patients. Those can be measured with DTI which provides the quantitative measurement and direction of water molecules diffusion.

It is used to visualize the white matter tract as a tractography. Fractional anisotropy (FA), a measure derived from DTI, reflects the degree of white matter fibers integrity. Correlation between cognitive performance and FA was proved in previous studies [48, 49]. One of the mechanism explaining this phenomenon is disconnection of regions important for cognitive processes secondary to the damage to white matter fibers. The significant role of corpus callosum fibers damage, principally in anterior part, was demonstrated [50–52]. This fact seems understandable due to the engagement of this area in connecting prefrontal regions, which are responsible for cognitive processes, especially operative memory and executive function. DTI technique is still developing. One of the novel method is High Angular Resolution Diffusion Imaging (HARDI), which enables analyzing the number of distinct diffusion orientations in the tissue. It reflects crossing the tracts. The lower number of diffusion directions in the frontal cortex predicted executive function deficit, independently from FA decrease [53].

Magnetization transfer ratio (MTR) is another parameter defining NABT abnormalities. MTI is a method used to obtain additional tissue contrast based on the exchange of magnetization between two proton groups – bound to macromolecules and free contained in the water. MTR is primarily determined by the content of myelin in the tissue, therefore it is a sensitive marker of axonal integrity. This ratio appeared to be more important factor determining cognitive impairment than brain volume, total lesion volume in T2-weighted images and cortical lesions [54, 55]. In addition, reduction of cortical MTR correlated with cognitive functioning in individuals with benign MS [56]. It was also proved, that MTR measured at the early stage of disease is a predictive factor for the development of cognitive impairment after a few years [57].

Interesting results were also obtained in researches employing <sup>1</sup>H-MRS to assess abnormalities in NABT. This technique is used to determine the metabolic composition in a selected region of the brain. The results indicate an association between decrease in N-acetylaspartate (NAA), a marker of neuronal integrity, and cognitive deterioration. Cognitively impaired individuals were characterized by decrease in NAA in some locations, for example frontal regions of white matter, regions around occipital horn of lateral ventricles, anterior part of cingulate cortex and right nucleus locus ceruleus, the latter one was related to attention deficit [58–61].

### **Cognitive impairment after CIS**

Cognitive dysfunction may also occur in the early stage of disease, including CIS [6, 8, 15, 17, 26, 62, 63]. As previously mentioned, it develops less frequently than in MS, still the profile of deterioration is similar. A form of the CIS has no effect on cognitive symptoms [26].

Most studies revealed no relation between cognitive impairment and demyelinating lesions in T2-weighted images [6, 7, 9, 62]. Various methods for evaluation of the lesions were used in these researches – the number of lesions, total lesion volume, meeting the criteria of dissemination in space (McDonald's criteria revised in 2005 [64]). However, in one study a correlation between cognitive functioning and total lesion volume in case of patients with acute optic neuritis was noticed [17]. It is proved

that the neurodegenerative processes reflected by brain atrophy have a crucial role for the induction of cognitive symptoms in MS. Nonetheless, a question whether this mechanism applies to the early stage of disease remains to consider. Brain tissue loss enhances with the disease duration, therefore atrophy is more pronounced at a later stage of MS [65]. Nevertheless, atrophy, primarily in the cerebral cortex, is observed even in patients who had a first episode of neurological symptoms caused by demyelination [66–68]. Khalil et al. did not confirm the hypothesis, that the early cognitive impairment results from neurodegenerative process reflected by brain atrophy. In this research cerebral cortex volume was a main predictive value for cognitive deterioration in individuals with MS, in contrast, this value did not correlate with cognitive functioning in patients after CIS [7]. In addition, correlation with brain volume was not observed in another research on the group of patients with MS at the early stage [49].

There are other structural abnormalities than T2 hyperintensities, T1 hypointensities and brain atrophy through the brain tissue which occur in MS. A few studies conducted so far detected damage to NABT after CIS similar to abnormalities noticed in MS. Decrease of NAA in brain was observed in this population with use of  $^1\text{H}$ -MRS [69–71]. Moreover, one study revealed increase of myo-inositol (density and activity of glial cells marker) in NABT [72]. MTR as well as FA, which are the sensitive indicators of brain tissue damage, were also found to be impaired – decreased MTR in NAWM and the reduction of FA in NAWG, subcortical nuclei and thalamus was noticed in patients after CIS [73, 74].

Only one research evaluating the relation between NABT abnormalities and cognitive function in CIS patients was conducted so far. The study revealed such correlation in case of cortical MTR while cerebral cortex atrophy was not related to cognitive performance [7]. It allows formulating the hypothesis that cognitive impairment at the early stage of disease are related to the neurodegenerative process, which is reflected primarily by NABT abnormalities rather than brain atrophy. However, this issue requires further investigation.

### **Influence of genetic factors on the course of MS and the occurrence of cognitive dysfunction**

Genetic contribution to MS susceptibility is known. However, estimated heritabilities are inconsistent – in Swedish population it was 64%, in Italian 48% and in Finnish 15% [75–77]. The experiments emerged more than 50 loci underlying the susceptibility and severity of disease [78, 79]. Most of them are genes encoding proteins of the immune system. The histocompatibility antigens allele *HLA-DRB1\*1501* carriers have an increased risk of MS development [80]. Other HLA loci-*A, B, C, DQA1* and *DQB1* are also correlated with MS, as well as genes associated with cytokines such as *IL7R*, *IL2RA* and other elements of inflammatory system [79, 81]. Glutathione S-transferase (GST) supergene family, which encodes isoenzymes involved in the removal of oxidative damage is another potential genetic factor associated with MS. Studies indicate that mutations in the *GST* gene, which reduce enzymatic activity of its protein, worsen the course of MS in patients with a disease duration of at least 10 years [82], while *GSTT1*

deletion increases the risk of developing MS [83]. Researches on the 19q13 region containing the gene encoding apolipoprotein E, which takes part in the regulation of brain homeostasis [84], revealed three alleles and 7 single nucleotide polymorphisms (SNP) associated with the course of disease and cognitive dysfunction [85–87].

Presence of *HLA-DRB1\*1501* allele is most precisely described genetic factor associated with MS. Despite number of studies it is not established whether this allele correlates with the severity of disease, including the occurrence of cognitive dysfunction. Depending on the analyzed population contradictory results were obtained – in the countries of Western Europe and Scandinavia correlation between presence of the allele and clinical course of MS was proved [88, 89], while corresponding relation was not found in the groups from North America and Australia [90, 91]. No similar studies on the population of Central and Eastern Europe were conducted. Available analysis of a large group of patients from the United States showed that the genotype *HLA-DRB1\*1501* is more common in female than male patients and is associated with an earlier onset of MS [92]. Its presence correlates with information processing speed and memory impairment. Moreover *HLA-DRB1\*1501* is related to increase of T2-lesions volume and reduction of NAA in NAWM, but not affecting NAWG [92].

Apolipoprotein E (APOE) gene polymorphism is another factor associated with cognitive functioning. Differences in three alleles – *APOE e2*, *e3* and *e4* alter protein structure and function. Presence of *APOE e4* is well known Alzheimer's disease risk factor [93]. Moreover, it correlates with cognitive function in MS patients [86]. *APOE e4* carriers have 6-fold increase in the risk of impairment in verbal learning [94]. In 30–40 years old patients *APOE e4* correlated with the occurrence and the severity of cognitive deficits in domains of learning and memory [95, 96]. The relation between the presence of *APOE e4* allele and level of NAA in NAWM was also analyzed. As in the case of allele *HLA-DRB1\*1501*, allele *e4* was associated with a significant decrease of NAA in NAWM, which is likely due to the increased degree of neuronal damage. In addition, 2-year follow-up study showed that *APOE e4* carriers had a significantly greater reduction of NAA in NAWM versus non-carriers [97].

## Conclusions

Understanding the nature of cognitive dysfunction in MS would be the next step of explaining the complex pathomechanism of disease development. The clinical data and demyelinating lesions provided by MRI do not reflect the occurrence and severity of cognitive deterioration, while it seems to be more related to neurodegenerative aspect of disease process than inflammatory activity. The application of modern MRI techniques contributed to improve the understanding of the mechanism responsible for the development of cognitive dysfunction in MS. Indeed, the role of abnormalities within NABT was revealed. Much attention is paid to the pathology of gray matter, both cortical lesions and cerebral cortex atrophy. Development of researches on the genetic background of MS resulted in some reports concerning relations between the genetic profile and cognitive dysfunction. The substrate of cognitive deterioration in MS has not been explained so far, thus there is a necessity for further investigation

on this issue. Neuroimaging evaluation as well as genetic and immunological factors should be taken into consideration as a predictors of MS form linked with cognitive symptoms.

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