Cognitive impairments in multiple sclerosis: A review

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Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Cognitive impairment (CI) may develop at any time during the course of the disease in the presence or absence of neurological disability. On the basis of comprehensive neuropsychological studies, there is now a consensus among investigators that 45 percent to 65 percent of MS patients suffer from some degree and form of cognitive difficulty. Features of CI include bradyphrenia; impaired attention, concentration and abstract reasoning; reduced manual speed and dexterity; deficits in memory retrieval; and language deficits in both the relapsing-remitting and progressive forms of MS. Impairments in all cognitive domains may result from the diffuse spread of microscopic pathology, although a preferential lobar distribution of plaques can present with a predominant deficit in the corresponding cognitive function. Nevertheless, the severity of CI best correlates with total microscopic and macroscopic disease burden of the brain as defined by recently developed magnetic resonance imaging (MRI) sequences. A disruption of connecting intercortical and subcortical pathways is likely to be the main cause of metabolic and functional abnormalities in neurons. However, a direct toxic effect of soluble inflammatory products may also compromise neuronal function and survival. Early treatment of MS with interferons and copaxone can prevent or delay the onset of both neurological and cognitive disabilities by reducing the inflammatory activity and damage in the CNS. Until more powerful neuroprotective agents become available, simple neuropsychological screening and cognitive rehabilitation for memory and language impairments will remain important components in the care of MS patients.

Key words: multiple sclerosis, cognitive impairments, neuropathology, neuroimaging

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), which affects over 250,000 Americans.[1] Although the etiology of MS remains unknown, both autoimmune and infectious mechanisms of plaque formation have been postulated.

Clinical course of MS

On the basis of an international survey of specialists, a distinction among four clinical courses, including (1) relapsing-remitting, (2) secondary progressive, (3) primary progressive, and (4) progressive-relapsing courses, has been recommended.[2] Although there are major differences not only in the clinical dynamics, but also in the spatial and temporal distribution of pathology, a progressive accumulation of disability characterizes all of the forms of MS. Motor, visual, coordination, and autonomic deficits are generally considered to be the major components of disability. However, affective and cognitive dysfunction may also develop and become incapacitating in a significant proportion of patients.

Measures of MS pathology by new MRI sequences

Conventional magnetic resonance imaging (MRI)

techniques (T1 weighted with and without contrast; T2 and proton-density weighted, fluid attenuation-inversion recovery) well describe the distribution and activity of plaques. However, these sequences cannot detect microscopic lesions in the normal-appearing white matter (NAWM), and neither can they assess global lesion load. Recently developed methods such as magnetization transfer imaging (MTI), MT ratio (MTR), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) reveal abnormalities in the NAWM, gray matter, and plaques in a more sensitive and specific manner.

MRI studies reveal that, although demyelinating lesions predominantly affect the white matter and the gray-white matter junction, lesions in the cortical and deep gray matter also may be visualized.[3-6] Prolongation in T1 and T2 relaxation times, reduced MTR values, and increased tissue water-diffusion coefficient in DWI suggest diffuse abnormalities in the NAWM of MS patients. The pathological correlates of these abnormalities include microscopic edema, demyelination, astrogliosis, and axonal loss.[7-10] MR spectroscopy studies confirm that significant degrees of axonal loss develop secondary to direct inflammation and Wallerian degeneration outside of plaques.[11] As a result of these degenerative changes, a progressive development of brain atrophy can be detected from the first onset of clinical symptoms.[7-13] Generally, the distribution of plaques detected by conventional MR imaging only weakly correlates with quantitative and qualitative features of clinical disability. Radiological and biochemical markers of axonal loss and measures of global (microscopic and macroscopic) disease correlate best with the clinical heterogeneity and severity of MS.[12,13]

Histologic heterogeneity of plaques and pathology in the gray matter

MS is a complex trait, with the involvement of several genes, each with relatively small effect. The genetic heterogeneity observed among families likely reflects a heterogeneous pathogenesis.[14] On the basis of myelin protein loss, oligodendrocyte destruction, and inflammatory marker profile in a series of biopsy and autopsy tissues, Lucchinetti *et al.*[15] defined four patterns of demyelination. Pattern I is characterized by prominent T cell and macrophage infiltration, whereas pattern II has an additional contribution of IgG and complement to myelin destruction. While both patterns I and II are consistent with an autoimmune processes, both patterns III and IV appear to be a primary oligodendrocytopathy. Mononuclear cell (MNC) infiltration, microglial activation, and oligodendrocyte apoptosis are seen in pattern III. In contrast, nonapoptotic oligodendrocyte death is associated with the MNC infiltration in pattern IV. Patterns I and II are typically found in patients who present with any of the known clinical subtypes. Pattern III is detected mostly in patients with a short duration of MS. Pattern IV has been noted only in three patients, all with primary progressive MS. In reviewing all lesion types among their patients, the authors suggest that an intraindividual homogeneity and interindividual heterogeneity of MS lesions exist.[15]

Although MS is classically considered to be a white matter disease, a significant microscopic pathology can be detected in the gray matter. There seems to be less inflammation within the gray matter, but demyelination is present in the small intracortical fibers. These lesions contain transected dendrites and axons, as well as apoptotic neurons, lending support to the hypothesis that demyelination, axonal or dendritic loss, and apoptosis of neurons in the gray matter may play a role in changes of higher cortical functions in MS.[16]

Summary

The above radiological and pathological studies suggest that MS represents a spectrum rather than a single entity of demyelinating disease in the CNS. Major individual differences exist in the dynamics and distribution of lesion evolution, causing a great variability in the clinical presentation. Recently developed radiological and biochemical methods provide markers to assess the global, macroscopic, and microscopic pathology in a more specific and sensitive manner than previous ones. These newer methods have enabled investigators to identify reliable correlates of not only neurological, but also neuropsychological, impairments.

Cognitive impairment in MS

Features of cognitive impairment in MS

Neuropsychological studies suggest that 45 percent to 65 percent of patients with MS have some cognitive impairment,[17-19] which usually includes bradyphrenia, impaired abstract thinking and information processing, and difficulties in attention, concentration, and memory retrieval. These symptoms can generally be observed in association with subcortical pathology of various origins and are collectively described under the term subcortical dementia.[17,20] Cortical aphasia, agnosia, and apraxia do not typically occur in patients with MS, but when they do, they may present relatively early during the disease.

Attention and memory problems in patients with mild cognitive impairment may be reversible after an acute exacerbation and can return to prior cognitive levels

upon remission.[21,22] Disturbances in sustained attention and multidirectional concentration have been found to be sensitive indicators of slowness in processing and cognitive decline.[23] Both impaired memory and slowed information processing contribute to a decreased verbal fluency, presenting mainly with slowness and naming difficulties.[23]

Problems with verbal memory and abstract reasoning seem to appear early in the course of MS, but may remain stable after a couple of years. These forms of cognitive dysfunction do not necessarily develop in parallel with other neurological deficits, but even as isolated symptoms may cause significant disturbances in everyday life.[24,25] Abnormalities in abstract thinking and executive function can be particularly disabling for patients whose jobs require high intellectual input. While short-term memory seems to be relatively preserved, working memory is often affected in MS. Retrieval of previously learned information is also frequently impaired, but recognition of such information is usually preserved.[19] However, a meta-analysis of 36 published papers on memory impairment in MS patients as compared to controls revealed significant abnormalities in all domains of memory function.[26]

The occurrence of abnormalities in visuospatial perception is somewhat underestimated by physicians, but nevertheless quite common in MS. It is not always possible to define with certainty whether these abnormalities are related to the primary visual and motor impairments or to a more complex abnormality in visuospatial processing.[17]

The combination of abnormalities in attention, working memory, speed of information processing, and visuospatial skills, along with physical disability, may significantly compromise the performance of complex tasks such as getting to a destination by driving a car.[27]

Because of the great interindividual variability in the total amount, distribution, and molecular nature of microscopic and macroscopic pathology, the clinical patterns of neurological and psychological deficits may greatly differ among patients. Cognitive impairment may appear to affect only certain domains of intellectual functioning in patients in an early stage of the disease, or in those with a preferential anatomical (*e.g.*, frontal or parieto-occipital) distribution of pathology. However, involvement of all cognitive domains (subcortical dementia) usually becomes apparent in late stages of intellectual deterioration, associated with inflammatory demyelination. Nevertheless, severe, global dementia that requires full supervision and assistance has been noted in only a small subgroup (5 percent to 10 percent) of MS patients.[19]

Neurological (visual, motor, coordination, sensory, or autonomous) components of disability may not always correlate with the degree or nature of cognitive deficits, although patients with more active and severe disease tend to have a higher frequency and severity of cognitive disease.[17,19] In the above-mentioned meta-analysis of studies on memory impairment,[26] neurological disability modestly correlated with memory deficits, the disease duration was only related to working memory, and the progressive course strongly correlated with short-term and working memory difficulties.

Generally, cognitive impairment in MS may develop at any time during the disease and can be associated with either mild or severe neurological disability.[19] Although patients with all progressive forms of MS tend to have cognitive impairment more often than those with a relapsing-remitting course, disease duration and disease course do not absolutely predict cognitive performance in individual patients.[1] Patients with severe clinical disability may not necessarily have any cognitive impairment. Finally, as mentioned above, cognitive impairment can fluctuate similarly to other components of neurological disability observed during relapses.

Correlation of cerebral pathology and metabolism with cognitive impairment

FLAIR is superior to conventional MRI sequences in revealing the extent and distribution of juxtacortical and cortical lesions, which correlate well with components of cognitive dysfunction.[3,4,28] Enlargement of ventricles and atrophy of corpus callosum also generally correlate well with cognitive dysfunction in several studies.[29-31] Measures of atrophy and axonal integrity are related to semantic fluency, sustained attention, and speed of information processing.[32] Lesions in the corpus callosum appear to be related to slowness of information processing,[17] impaired verbal fluency,[33] visuospatial difficulties[34] and signs of interhemispheric disconnection.[35]

Swirsky-Sacchetti *et al.*[36] conducted a detailed MRI and neuropsychological study to correlate measures of total lesion area, ventricular-brain ratio, and size of the corpus callosum with cognitive function in frontal, temporal, and parieto-occipital regions. Generalized measures of cerebral involvement correlated well with neuropsychological deficits, with the total lesion area being the strongest predictor of cognitive impairment. Multiple regression analysis revealed that left frontal lobe involvement correlated with impaired abstract problem-solving, memory, and world fluency. Left parieto-occipital lesions predicted deficits in verbal learning and visuospatial skills.[36] In other studies, frontal lobe lesions also correlated with perseverative responses and deficits in executive function.[35,37] Sperling *et al.*[38] investigated the relationship between the MRI-assessed regional lesion burden and cognitive performance over a four-year

follow-up period. The authors consistently found a propensity of MS lesions to be in the frontal and parietal white matter in association with impairment of sustained complex attention and working verbal memory at baseline, one-year, and four-year follow-up.

Conventional MRI techniques generally demonstrate that cognitive impairment in MS is related to the lesion load, but this relationship is weak.[39] Measures of total brain disease by nonconventional techniques such as MTR of the whole brain, MTR of NAWM and lesions, and hypointense lesion load on T1 weighted scans may provide better anatomical correlates of cognitive (and neurological) disability.[39,40] These studies establish that the overall macroscopic and microscopic pathology is more important than the corresponding regional brain disease in defining deficits of selective cognitive domains.[6,10,41]

In addition to classical MRI modalities, functional MRI (fMRI), proton emission tomography (PET), and single photon emission computer tomography (SPECT) are gaining importance in studying metabolic aspects of CNS diseases. Jeffrey *et al.*[42] studied three cognitively impaired MS patients. Two of them underwent PET scans, which demonstrated profound cortical hypometabolism adjacent to juxtacortical white matter lesions seen on MRI scans. This study also showed that intellectual deterioration may occur and rapidly progress in the absence of motor disability. Sun *et al.*[43] studied cerebral blood flow and oxygen metabolism in the brain of 20 MS patients. The authors found a strong correlation between markers of cerebral hypometabolism in gray and white matter, lesion load on MRI, and clinical disability in MS patients. Another PET study by Blinkenberg *et al.*[44] similarly demonstrated a global and regional decrease in cerebral glucose metabolism of MS patients compared to controls. The glucose metabolism abnormality correlated with the total lesion load on MRI as well as with cognitive dysfunction.

PET studies have significantly contributed to a better definition of the anatomical substrates of memory problems. These studies have shown that (in contrast to previous beliefs) not only is the hippocampus involved in the initial coding and retrieval of long-term memory, but also an entire network of structures is activated during long-term and working memory tasks. In MS, bilateral reduction of metabolism may be seen in the frontal cortical regions and hippocampus, which are directly connected with the anterior thalamic nuclei.[44] The bidirectional connections of the frontal lobe (thalamic nuclei) cerebral cortex are disrupted by the widespread white matter lesions in MS, which also result in a reduction of glucose metabolism in the thalamic nuclei of patients with cognitive dysfunction and high lesion burden.

Effects of emotional changes on clinical disability and quality of life

Psychological disability in MS includes emotional changes such as euphoria, depression, bipolar disorder, suicidal ideation, grief, antisocial behavior, psychosis, and emotional lability. These symptoms interfere with everyday activities and negatively influence quality of life in many different ways, including the amplification of the perception and effect of cognitive abnormalities.

Preceding MS, the lifetime prevalence of depression is estimated to be around 15 percent, similar to that in the general population.[19,45] However, this figure increases to 50 percent after the onset of MS. The point prevalence of depression among MS patients attending the clinic has been assessed to be 14 percent as compared to 2 percent of the general population.[45] Of note, depression in MS patients is more common than in any other patients with chronic diseases or similarly disabling neurological conditions. Consequently, suicide as a cause of death increases to a 7.5 times higher rate in MS patients as compared to the general population.[46] In contrast, bipolar disorder is much less common in MS.

Causes of depression may be related to several mechanisms, including the disruption of normal anatomy by lesions, changes in neurotransmitter production, and alteration of the neuroendocrine and neuroimmune pathways. Recent MRI studies correlated cortical gray matter atrophy with depression observed in MS.[3] Secondary reaction to disability and activity of disease or medication side effects may also contribute to severe depression.[19,47]

Most studies addressing the relationship between depression and cognitive impairment in MS suggest that there is little or no relationship between them.[19,48,49] However, a meta-analysis by Thronton and Naftail[26] reveals a strong correlation between depression and working memory, but no relationship between depression and short-term or long-term memory.

Euphoria, an inappropriate expression of optimism and happiness, is often associated with other signs of emotional disinhibition. Euphoria affects less than 10 percent of patients with MS and is usually associated with diffuse and severe pathology, advanced physical disability, and dementia. However, an exaggerated expression of optimism in some patients with MS may only serve as a coping mechanism to hide the overwhelming negative emotions triggered by the physical condition.[19]

Antisocial behavior and psychosis seldom occur in MS. These symptoms may present as a transient episode accompanying an exacerbation of the disease or as a more sustained abnormality, even during stable periods between relapses. In severe cases of these symptoms, psychiatric treatment may be necessary.

The relationship of stress, anxiety, and fatigue with cognitive dysfunction in MS remains controversial or rejected. However, any of these symptoms can disturb everyday life, and may worsen the subjective judgement of disability and physical or cognitive performance in individuals with or without MS.[19]

Neuropsychologic tests

Formal assessment of cognitive dysfunction is not routinely obtained in every MS patient. Costs prohibit widespread use of thorough testing because a complete battery of neuropsychologic tests is time-consuming and requires trained personnel.[17,50]

Screening tools for physicians taking care of MS patients with possible cognitive impairment are not yet definitively established, but some tests seem to be sensitive enough to indicate when further neuropsychologic testing is necessary.[38] Of note, the Paced Auditory Serial Addition Test (PASAT), a measure of complex attention and concentration, is part of the recently developed and validated Multiple Sclerosis Functional Composite (MSFC),[51] recommended by the National Multiple Sclerosis Society as a new outcome measure for clinical trials. Although no single informative test alone can substitute for a full neuropsychologic assessment, the MSFC is proven to be clinically relevant, easy to administer, and useful in clinical practice.

Genetic factors conferring risk to developing cognitive impairment

Four comprehensive genome scans performed in affected sib pairs and multiplex families revealed linkage to multiple susceptibility loci.[52-55] Several provisional sites were reported, but only the 6p21 (MHC complex), 5p15-5q13, 17q22, and 19q13 regions were consistently positive in more than one study.[52-55] An intensive search to identify MS-associated single nucleotide polymorphisms within coding and regulatory regions of candidate genes is underway. The influence of apolipoprotein-E (ApoE) polymorphisms on susceptibility and course of the disease has been intensively investigated.[56,57] Oliveri *et al*.[58] studied the -491A/T polymorphism in the regulatory region of ApoE, which has been associated with an increased risk for developing Alzheimer's disease. By revealing that the AA homozygous state of this site is associated with cognitive decline in MS, the study suggests a general role of this polymorphism in defining the clinical presentation of various pathological conditions in the CNS.

Therapy

Standard therapies of relapsing-remitting and secondary progressive MS include various preparations of interferon-β1a, interferon-β1b, and copaxone. All these agents seem to have a favorable effect on relapse rate, disease progression, MRI measures of lesion activity and load, and brain atrophy.[59-63] Although the interferon-β preparations and glatiramer acetate act through different targets of immunopathogenesis, their overall benefit is quantitatively comparable. An early initiation and long-term administration of these immune modulants is expected to prevent or delay the occurrence of cognitive impairment in MS. Interferon-β1a (Avonex) has been shown to slow progression of cognitive impairment (information processing, learning and memory, visuospatial abilities, and problem-solving) similar to that observed in previous studies, focusing on neurologic impairments in patients with relapsing-remitting MS.[64] Studies are underway to assess objectively the impact of other interferons and copaxone on neuropsychological function.[65,66]

Symptomatic treatments of cognitive impairment in MS have generally been unsuccessful. Studies on 4-aminopyridine, a potassium channel blocker that improves nerve conduction, showed little benefit on cognitive functions in MS.[67] Tacrine HCl and donepezil HCl are cholinergic agents approved for the treatment of Alzheimer's disease, and also have been tested in several studies of MS. In a short-term, open-label trial, donepezil HCl appeared promising in improving several cognitive deficits, such as attention, memory, and executive functioning.[68]

Cognitive rehabilitation is an area that has not been much explored in MS. Two frequently tried strategies (mostly in traumatic brain injury) attempt to regain function by exploring plasticity of the brain, or by teaching compensatory mechanisms for the substitution of lost function.[19] Although some initial attempts provided promising results, the scientific evidence for the effectiveness of these methods is limited and requires further investigation.

Pharmacological management of emotional changes include the standard mood stabilizing agents (lithium carbonate, valproic acid), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, buproprion HCl, trazadone), and psychotherapy.[19]

Summary

Cognitive impairment is a significant component of disability in MS and affects more than half of the patients. The distribution and severity of microscopic and macroscopic pathology seem to best correlate with measures of neuropsychological disability. Disconnection of interneuronal networks in the cortex, juxtacortical regions, and

subcortical white matter as well as direct neurotoxic effects of soluble inflammatory products may progressively compromise neuronal function and cognitive performance. A successful treatment of the underlying disease process by recently available immune modulators is expected to have a beneficial influence on the development of not only neurological, but also neuropsychological, disability.

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