

Cognition, Depression and Fatigue in Multiple Sclerosis

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Multiple sclerosis (MS) is the most frequent central nervous system (CNS) disease of early and mid adulthood, 20-40 years of age,¹ affecting approximately 85,000 people in the UK.²

The various neurological symptoms associated with MS result from the neurological damage that occurs throughout the CNS, brain and spinal cord.³ MS is a heterogeneous disease, with substantial variability in the clinical course and symptoms among individual sufferers.⁴

Often overlooked are the multiple neuropsychological symptoms associated with MS, including cognitive dysfunction, fatigue and depression. Neuropsychological disorders are prevalent in MS, however, the effect of these symptoms has been underestimated and neglected in the past.⁵ It is, however, now recognised that these symptoms are linked to considerable disability and impairment of daily living. Depression and fatigue, for example, have been shown to be significant and independent predictors of quality of life (QoL).⁶ Early identification and management of cognitive dysfunction, fatigue and depression may have a significant impact on patients' work and social relationships, and overall QoL.

Impact of neuropsychological symptoms

Cognitive impairment

Cognitive impairment occurs in between 45% and 65% of MS sufferers⁷ and can present in patients at any time during their disease process from diagnosis. The severity of cognitive dysfunction can vary from mild to severe and the most frequently affected cognitive domains are memory, attention, information processing, and executive function.^{3,8} Cognitive impairment has a tremendous impact on patients' lives over the long-term, mainly due to the impaired information processing, lack of attention/ability to concentrate, and decline in recent memory.⁹ It can also lead to significant restrictions in the intellectual abilities of patients.¹⁰ Furthermore, cognitive impairment may affect driving performance.¹¹

Cognitive impairment may manifest early in the disease course prior to physical disability, and although it worsens with disease progression it is neither predictable nor linear. It has been estimated, however, that following a new diagnosis of MS, the prevalence of moderate and severe cognitive dysfunction doubles every four years.¹²

Several screening tests are available for diagnosing and assessing cognition and include a core battery of neuropsychological tests e.g. attention/concentration, memory executive functions etc. Cognitive testing in

patients with MS, however, is expensive and complex, and is complicated by the lack of standardised testing.⁵

Fatigue

Fatigue is extremely common in MS and is experienced by 78%-91% of patients.¹³⁻¹⁵ Furthermore, the majority of patients with MS (up to 69%) consider fatigue to be one of the most debilitating aspects of the disease.¹³⁻¹⁵ Fatigue is a multi-dimensional symptom and is characterised by an overwhelming sense of tiredness, a feeling of complete exhaustion, or a total lack of physical or mental energy, and is often the first noticeable sign that patients with MS experience.^{13,16} Fatigue in MS is very different from that experienced by healthy individuals as it has a tremendous affect on physical and cognitive functioning, and is known to be exacerbated by heat.^{13,17} Fatigue can be so severe as to affect work and social relations and daily mental and physical activities,¹⁸ and is a major reason cited for unemployment among patients with MS.¹⁹ Fatigue, however, is a subjective symptom that varies from patient to patient. Consequently, it can be difficult to measure. Although assessment tools such as the Fatigue Impact Scale (FIS), the Fatigue Severity Scale (FSS), and the Expanded Disability Status Scale (EDSS) are available for use, in clinical practice they tend to be subjective, self reported questionnaires rather than objective measures of fatigue.²⁰

Depression

Major depression is common in MS, with a lifetime prevalence of up to 50%.²¹ The annual prevalence of major depression is much higher in patients with MS aged between 18-45 years old (25%)²² than the general population (6%).²³ Depression is usually diagnosed early in the

course of the disease and is associated with increased suicide rates (1.95% to 18.5%).^{21,24} The presence of depression can reduce adherence to treatment and seriously affect patient self care.¹⁰ The high incidence of depression and the increased risk of suicide in depressed patients with MS make it very important to actively identify and treat depression. There are several questionnaire based assessments tools available that identify depression, including the Hamilton Rating Scale for Depression (HRSD).⁶ A diagnosis of major depression must include being sad, depressed mood, and/or loss of interest and pleasure in usual activities.²⁵

Causes of neuropsychological symptoms

Cognition, fatigue and depression all present as a direct result of the CNS damage that occurs in MS. Structural changes in the brain are responsible for cognitive decline. Cognitive impairment has been shown to be linked to white matter disease within the cerebral hemispheres of MS sufferers. The deficits in cognitive functioning have been shown to correlate with brain lesions²⁶ and atrophy, using magnetic resonance imaging (MRI).²⁷ The extent of cognitive decline is dependant on lesion location and size, particularly in the frontal lobes.²⁸

Although the aetiology of depression in MS remains unclear, it too is linked directly to brain lesions and atrophy. Furthermore, it appears to be associated with lesions in specific areas of the brain, in particular the left anterior temporal/parietal regions.²⁵ MRI has also shown that there is a correlation between global brain volume loss and the incidence of depression.²⁹ Psychosocial factors such as illness, intrusiveness and the burden of the disease also have an impact on depression in chronic disease such as MS.

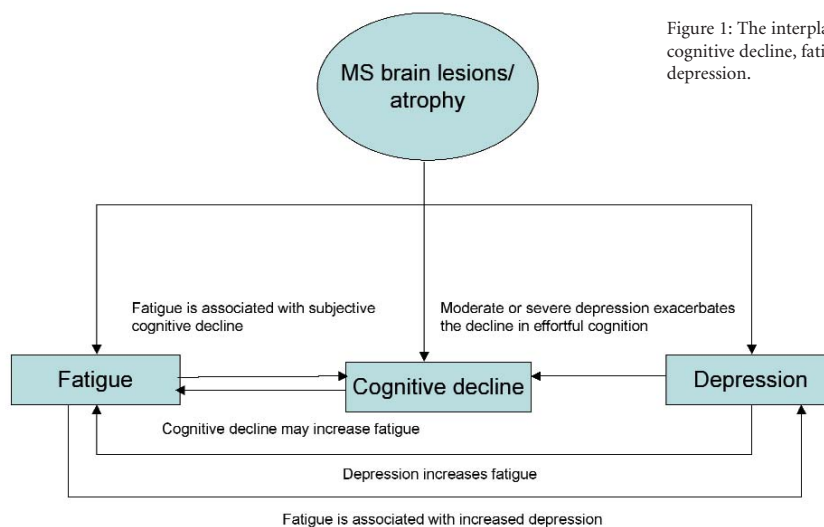


Figure 1: The interplay between cognitive decline, fatigue and depression.

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The underlying pathogenesis of fatigue in MS is the least well understood of the neuropsychological symptoms. Fatigue may be caused by the disease process (primary fatigue) or by other problems such as insomnia, infections, or psychological reasons i.e. coping with the disease (secondary fatigue).²⁰ There is some evidence from neuroimaging that suggests that fatigue is associated with brain atrophy³⁰ and diffuse axon damage in some patients.³¹

Complex interrelation between neuropsychological symptoms

There is a complex interplay between cognitive impairment, fatigue and depression in patients with MS (Figure 1). It is recognised that healthy people with depression are susceptible to cognitive deficits.²⁵ Despite this and rather curiously, most early studies showed no correlation between depression and cognitive decline in MS.²⁵ These early studies, however, focussed on the effect of depression on cognitive performance.²⁵ More recent studies seem to offer an explanation for these early findings.³²⁻³⁴ These recent studies suggest that in MS, cognitive performance may be unaffected and that effortful aspects of cognition, rather than automatic information processing, are influenced by moderate or severe depression. Consequently, areas of cognition that require attention such as tests of information processing, working memory and executive functioning are affected by depression, while performance often remains normal.²⁵ This is supported by Diamond et al who have shown that slower information processing correlates with higher levels of depressed mood.³⁵ A significant degree of depression, however, must be present before there is any effect on cognition.³⁶

There is also evidence showing that depression has an effect on fatigue in MS. One study has demonstrated a significant correlation between fatigue and mood level, and suggests that mental rather than physical fatigue is affected by the presence of depression.³⁷ Furthermore, treating depression seems to have a positive effect on subjective measures of fatigue.³⁸

The link between fatigue and cognitive decline is less clear; however, there is likely to be an interaction between the two symptoms.⁵ There is a strong association between self reported fatigue and a decline in subjective, but not objective, measures of cognition.³⁹ Indeed, many patients report that their cognitive performance is reduced by fatigue.⁴⁰ One recent study, however, has shown a correlation between fatigue and slower information processing using an objective measure of cognition, the California Verbal Learning Test (CVLT).³⁵ It is also possible that cognitive impairment may increase fatigue.⁵

Managing neuropsychological symptoms

Clearly cognition, depression and fatigue have a tremendous impact on patients' QoL and

everyday living. It is important, therefore, to detect and treat each of these conditions early in MS. Treating depression and fatigue is imperative not only because they are both common in MS and have a huge affect on the lives of sufferers, but also because treatment of these symptoms is likely to have a positive impact on cognitive function. The interplay between these neuropsychological symptoms requires a multi-modal approach to treatment. Careful monitoring and individualisation of pharmacological and non-pharmacological interventions is necessary in order to manage the neuropsychological symptoms of MS.

Cognitive decline

There are currently no approved medications for treating cognitive decline in MS; however, treatment of underlying disease with disease-modifying drugs has been shown in the case of one drug to slow the progression of cognitive decline.⁴¹ Four disease-modifying agents are currently available for the treatment of relapsing MS, interferon beta-1a intramuscular (IFN β -1a-IM), interferon beta-1b (IFN β -1b), glatiramer acetate, and interferon beta-1a subcutaneous (IFN β -1a-SC). IFN β -1a-IM is the first disease-modifying medication to demonstrate significant benefits on several measures of cognition in a large, controlled clinical trial. In a Phase III study, 166 patients with MS received IFN β -1a-IM 30 μ g or placebo for two years.⁴¹ Patients received a comprehensive and a brief neuropsychological battery. Patients treated with IFN β -1a-IM performed significantly better than those receiving placebo on tests of information processing and learning/memory ($P=0.011$), with a positive trend in visuospatial abilities and problem solving. Patients in the IFN β -1a-IM treatment group also showed a significant delay in sustained deterioration in the Paced Auditory Serial Addition Test (PASAT) processing rate, compared to placebo ($P=0.023$). Overall, a 47% reduction in the risk of cognitive deterioration was observed with IFN β -1a-IM. In the same study, IFN β -1a-IM reduced the rate of brain atrophy by 55% during the second year of treatment. Both glatiramer and IFN β -1b have failed to show such benefits in the most susceptible areas of cognition in well controlled trials^{42,43} and there are no reports of the effects of IFN β -1a-SC on cognitive impairment.⁴²

Cognitive dysfunction should also be managed with non-pharmacological interventions such as cognitive rehabilitation, counselling, education and lifestyle changes. Cognitive rehabilitation includes skills retraining and compensatory approaches, which allow patients to manage memory and recall better. Specific attention-training and neuropsychological counselling for example can improve cognitive performance.⁵ Education will allow patients to better understand their condition and recognise the neuropsychological symptoms if and when they occur. A large-scale ran-

domised controlled trial in older adults with cognitive impairment has shown that cognitive training delays cognitive and functional decline over a five-year follow-up.⁴⁴ This provides support that cognitive training is a potentially effective method of delaying cognitive decline in people with cognitive impairment, including in MS.

Interestingly, exercise may have a positive effect on cognition. One study in healthy older women showed that long-term regular physical activity, including walking, is associated with significantly better cognitive function and less cognitive decline. In another study in patients with dementia, regular physical activity was shown to be a potent protective factor against cognitive decline.⁴⁵ Although this has not been assessed in patients with MS, exercise may help improve or stop the progress of cognitive impairment.

Depression

Moderate and severe depression has a negative effect on cognitive function so its treatment should improve cognitive impairment. With the depression treated and cognition improved, patients should then be able to take on board strategies for dealing with cognitive impairment such as memory loss, which would then help improve general well-being and QoL.

Depression contributes significantly to fatigue in MS, and it has been shown that treating depression reduces fatigue.⁴⁶ In a study of patients with relapsing MS and moderate to severe depression, after 16-week of treatment for depression (individual cognitive behavioural therapy, group psychotherapy, or sertraline), scores on the total fatigue assessment instrument and the global fatigue severity subscale were significantly reduced over the course of treatment ($p<0.02$). These findings suggest that treating depression is associated with reductions in the severity of fatigue, and that this relationship is due primarily to treatment related changes in mood.

Interestingly, the treatment of depression (cognitive behavioural therapy, group psychotherapy and anti-depressant therapy) has been shown to decrease the production of the pro-inflammatory cytokine IFN- γ in patients with relapsing-remitting MS.⁴⁶ This finding highlights the need for more research into the potential disease modifying properties associated with the treatment of depression in MS.

Fatigue

Owing to the complex aetiology of fatigue a multidisciplinary approach to treatment is required that includes a range of pharmacological and non-pharmacological interventions. Drug treatments include amantadine, modafinil and 4-aminopyridine.¹⁰ Amantadine is the treatment of first choice in most patients.¹⁰ Non-pharmacological interventions include regular exercise programmes, energy conservation strategies, and hyperthermia

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avoidance. Once fatigue has been addressed it may be possible to obtain a baseline for cognitive function that will enable certain strategies to be applied in order to manage any cognition decline.

Treating fatigue has been shown to improve depression and cognition. In a study investigating the effects of the wake promoting drug modafinil in other wise healthy patients with depression, significant improvements in fatigue (VASE, FSI) were observed.⁴⁸ This corresponded with significant improvements in depression (HDRS, BDI, CGIS), as well as to significant gains in cognition using the Stroop Interference Test. These effects in healthy depressed patients are also likely to be observed in depressed patients with MS.

The effect of fatigue management and energy conservation has also been evaluated.⁴⁹ In one study, patients with MS were assessed immedi-

ately after attending a fatigue management course and then seven to nine months later. The total score on the Modified Fatigue Impact Scale (MFIS) showed significant improvements at both time points. Interestingly, the cognitive subscores of the MFIS were also significantly improved. Furthermore, the depression score decreased significantly to a normal level at the end of training, and at the seven to nine month follow-up. This research demonstrates that fatigue management not only has a positive effect on fatigue in MS, but also on cognition and depression.

Conclusions

Neuropsychological symptoms in MS include cognitive impairment, depression and fatigue. These symptoms, experienced very frequently by MS sufferers, result directly from the brain

lesions and atrophy that are characteristic of the underlying disease pathophysiology. Furthermore, there is a complex interplay between cognition, depression and fatigue; with each symptom impacting negatively on the others. These neuropsychological symptoms impinge tremendously on the social and working lives of MS sufferers. Consequently, it is imperative to identify and treat these symptoms early in the course of MS. Treating one symptom can also result in significant improvements in the others. For example, effectively treating fatigue also has a positive effect on depression and cognition. Adopting a multi-modal approach to treating these neuropsychological symptoms that incorporates both pharmacological and non-pharmacological interventions, will have a significant impact on patients' well being and QoL.

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