Brain Volumetric Assessment and its Relation to Cognition and Fatigue in Multiple Sclerosis

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Abstract: *Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the CNS. MS is believed to impact 900, 000 patients in the USA. MS negatively impacts quality of life by affecting motor functions, cognitive abilities, and employment in those aged 20 to 30. New imaging modalities aided in measuring brain volume with MRI-related tools. MRI-measured brain volume loss was found to be correlated with atrophy and the degree of impairment in MS. Early studies of MS confirmed both white and grey matter loss. Grey matter damage may precede white matter damage. Furthermore, grey matter volume reduction is more pronounced and is more correlated to clinical outcomes than white matter. More advanced MRI techniques for studying microstructural brain alterations and ultra-high-field MRI for evaluating cognitive deficits in MS patients will help researchers better understand the disease's cognitive abnormalities in MS patients. The next and most challenging task is to create testable, physiologically informed models of disease-related cognitive deficits using the extensive multimodality imaging data. As MRI technology advances, researchers are more interested in examining specific brain regions and their relevance to MS fatigue. Many areas were identified in the frontal and parietal cortices, thalami, and basal ganglia. The fronto-striatal network and the cortico-cortical network have all been found to play an important role in MS-related fatigue.*

Keywords: Multiple Sclerosis, Brain volume, Cognition, Fatigue

1. Introduction

Inflammatory demyelination and axonal transection are hallmarks of multiple sclerosis (MS). Severed terminals of neurons define axonal transection and indicate persistent neurologic damage. In the United States, nearly 900, 000 people are believed to suffer from multiple sclerosis. (1–3) . MS is most often diagnosed in individuals between the ages of 20 and 30 and frequently impairs physical function, cognition, quality of life, and employment.

Parallel to developments in our knowledge of neurodegenerative causes, breakthroughs in imaging methods have permitted evaluation of brain and spinal cord volumes using MRI. Although volume loss detected by MRI cannot be equated with atrophy (4) , which is defined as permanent and pathological tissue loss, alterations in certain MRI measurements are related to atrophy (Popescu et al., 2016) and the severity of disability in MS.

Cognitive dysfunction in MS has an impact on many elements of everyday life, including involvement in social activities, driving ability, and work status; it also has a significant negative impact on health-related quality of life. IPS and visuospatial learning, for example, have been linked to poor driving performance in approximately 20% of people with multiple sclerosis (MS). (5, 6) , while deterioration of employment status in MS is four times more likely when IPS and verbal learning are reduced over time. (7)

Scientists and caregivers continue to pay close attention to MS fatigue (8) . For the first time, Freal et al. found that 78 percent of MS patients they assessed expressed exhaustion as their most vexing symptom (8) . Following these startling

results, an expanding body of research has shown that fatigue is prevalent patients with MS, with 70%–90% of patients experiencing it at some point in time (8–10) .

We will discuss the era of brain volumetric scans as a new trend in MS patient assessment and its implications for two of the primary MS symptoms, cognitive impairment and fatigue, in this review.

2. Volumetric assessment in MS

Although volume measurements are not included in the MS diagnostic criteria (11) or disease course classification (12) , a body of data supporting their efficacy for early assessment and prediction of disease progress has been slowly developing, coupled with improvements in technique that may allow wider application of these measurements in clinical practice (13)

2.1. Multiple sclerosis severity is determined by measuring the total brain volume.

Clinical studies investigating the correlates of brain atrophy in multiple sclerosis first focused on persons with established disease and considerable clinical symptoms, particularly in the cognitive domain (14) . These findings showed that neurodegenerative processes occur in the early stages of MS (15, 16)

2.2. MS severity may be defined and predicted using tissue-and region-specific brain volumetric measurements.

Early investigations of brain white and grey matter alterations in MS patients showed both white and grey

matter loss early in the illness course (17, 18) . Grey matter injury may arise before or independently of white matter abnormalities (19) . Additional longitudinal studies revealed that grey matter volume diminishes more rapidly than white matter volume, and that grey matter injury has a greater impact on clinical outcomes than white matter injury (20, 21)

2.3. Technical issues in volumetric brain imaging

Image capture and quantification may have an impact on the accuracy of brain and spinal cord volume estimates. Technical issues are addressed in the following (22)

2.3.1. Protocols for volumetric data acquisition
The acquisition parameters are normally chosen based on the visual contrast of the image as assessed by a neuroradiologist. Cross-sectional and longitudinal comparisons are less reliable because of changes in the scan parameters that are prevalent in the clinical situation. Additionally, MRI image contrast is strongly influenced by the age of the group being scanned. (23)

2.3.2. Variations between MRI scanners
Any MRI-derived parameter is intrinsically variable, even under controlled technical and physiological settings. (24, 25) . Global estimations, such as the volume of the whole brain, are the least variable (1%) (26) , but smaller regions, like the amygdala, have a higher degree of variability in their readings (26) . It's important to take into account such variability, since changes smaller than the expected variability cannot be consistently detected. Small grey matter structures and short follow-up periods are especially affected by this limitation. (27)

2.4. Volumetry tools

As MRI reading services have become more common in the past decade, several organisations have begun to provide their own software to measure atrophy. All four software packages approved for use in Europe have been approved by the Food and Drug Administration for use in the United States. For cross-sectional volumes, Nifty Segment software is used, while Jacobian integration software is used to estimate longitudinal changes in grey and white matter. Cross-sectional and longitudinal atrophy measurements may be made using NeuroQuant (CorTechs Labs). (28) . NeuroQuant expands on previously reported approaches (29) . A software library for neuroimaging analysis and atrophy quantification, as well as the Lesion Segmentation Tool for automated lesion segmentation, form the basis of Biometrica MS (Jung Diagnostics) (30) . An MRI scanner linked with a Quantib Brain (Quantib) platform enables the measurement of cross-sectional and long-term changes in brain volume. As far as remote analysis services go, IcoBrain, Biometrica, and Quantib Brain all provide this option, while NeuroQuant may be operated either remotely or locally. Biometrica is the only package that does not have the CE mark and FDA approval. They show that the software may be used as a medical device because of the uniformity in procedures and outcomes. (31)

3. Cognition and multiple sclerosis

As the disease progresses, the cognitive abilities of those with MS are significantly impaired. A neuropsychological impairment in one or more cognitive areas affects around 40 % to 70 % of patients with multiple sclerosis. (32) . Multiple sclerosis (MS) is characterized by a progressive loss of cognitive function. MS patients in the 'preclinical' stages (i. e., those with radio logically isolated syndrome (RIS)), clinically isolated syndrome (CIS), and in the early stages of RRMS have shown signs of it. (16) . Cognitive impairment is more prevalent in the progressive forms (32, 33) Cognitive impairment increases from 30–40 percent in the early phases (such as RIS, CIS, and the early stages of RRMS) to 80–90 percent in the more severe stages and progressive forms (PPMS and SPMS) (33)

3.1. Cognition in relation to brain imaging

3.1.1. Cognition-related neuroimaging research
It's important to note that MS is at the forefront of new and novel MRI technology, which provides a wide range of approaches for assessing cognitive impairments linked to MS. (32) . Early research linked cognitive deficits to increased lesion load (34) , and later research showed the relevance of white matter lesion location and microstructural damage (35) , grey matter lesions, (36) cortical (37) and subcortical (38) . Additional pathways for studying MS cognitive problems will be opened up by advances in ultra-high-field MRI, myelin imaging, demyelination/ remyelination imaging, and innovative MRI techniques for evaluating microstructural brain changes. (39, 40) . An important but challenging next step is integrating multimodality imaging data into testable and physiologically informed models of disease-related cognitive deficits. Experts in imaging modalities, neuroscience and cognition will have to work together to achieve this aim.

3.1.2. Assessing the likelihood of future cognitive impairment.
T2 lesion volume, cerebral atrophy, microstructure damage, and cortical lesions have all been shown to be linked with cognitive impairment in long-term MRI research. (41, 42) Further prospective multimodality neuroimaging research with large representative samples is necessary to create risk algorithms for cognitive decline despite its time and expense requirements. Such algorithms should be tested in confirmation samples for specificity and sensitivity, therefore confirming their clinical relevance, when paired with demographic, reserve, and clinical variables. (43) . Research and practice in early cognitive intervention may benefit from accurate algorithms that aid in early treatment decisions (e. g., the aggressiveness of DMT). Practicality of MRI-based risk algorithms is presently hampered by the capacity to undertake sophisticated scanning sequences during clinical MRI and the availability of specialized skills needed to extract quantitative MRI measures. In fact, clinicians seldom have access to even the most basic information, such as total brain atrophy and the amount of T2 lesional volume. It is hoped that by providing clinicians with brain atrophy analysis services, these organizations would be able to integrate atrophy consideration into standard clinical therapy. (44)

4. Fatigue and MS

4.1. A quick summary of the pathophysiology of fatigue

Due to the diverse nature of MS fatigue, investigators encounter problems in clarifying its underlying causes. These symptoms may be caused by morphological or functional brain abnormalities, as well as by neurochemical imbalances and dysfunctions in the brain's endocrine and immunological systems as well as by involvement in the peripheral nervous system of the sufferer. In addition, some research has explored the impact of clinical factors on the development of fatigue. (45)

4.2. Correlates of fatigue in patients with multiple sclerosis

It is still uncertain if MS related fatigue is a unique phenomenon or a syndrome that is related with or influenced by a range of clinical characteristics. While some authors have claimed that motor impairment may have a crucial role on the appearance of fatigue (46, 47) , others have argued against this hypothesis (weak association: (48, 49) ; no association: (50, 51)); This discrepancy may be explained in part by the fact that these investigations vary in terms of cohort characteristics, assessment approaches, and study methodology.

4.3. The corticostriatothalamocortical loop and MS fatigue

The remarkable developments in neuroimaging methods during the past decade have enabled a thorough evaluation of CNS disorders. This kind of investigation is not only beneficial, but also critical for improving our knowledge of the different pathophysiological processes that remain unresolved. In the area of multiple sclerosis, Numerous publications explored the influence of grey and white matter abnormalities, such as lesion load and brain atrophy, in the development of fatigue. While some writers demonstrated a positive link (52), others did not. (53–55) . Such disappointing findings could be explained by the fact that the symptoms appear to be caused by localised abnormalities rather than broad brain malfunction. From this vantage point, more complicated anatomical and functional MRI techniques may result in more positive outcomes. For example, magnetization transfer imaging and diffusion tensor imaging may be used to measure myelin density and fibre integrity. Additionally, applying functional MRI at rest or while performing a physical or mental task, it is now conceivable to study regional brain activation patterns and functional linkages. Proton magnetic resonance spectroscopy may also be used to detect disorders in the healthy white matter (56) .

Conclusion

MS is a common autoimmune illness that causes neuroinflammation and neurodegeneration in the central nervous system. Volumetry assessment technologies are rapidly changing, and there are a number of efforts underway to increase their clinical value and reliability. Fatigue and cognitive impairment are two of the most prevalent symptoms of MS, and research suggests that they are linked to a reduction in brain capacity on a global and regional scale.

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