Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex illness characterized by a range of symptoms, including fatigue, malaise, muscle pain, headaches, sleep disturbances, and cognitive disorders. It has been reported that 89% of patients with ME/CFS have cognitive disorders like concentration problems, deficits in attention and reaction time, and difficulties in processing complex information and free memory recall. In this study, the Australian authors used diffusion tensor imaging (DTI) parameters to investigate microstructural abnormalities of brain tissue in individuals diagnosed with ME/CFS.

The severity of ME/CFS has been classified according to the Fukuda criteria, the Canadian Consensus Criteria (CCC), and the International Consensus Criteria (ICC). The Fukuda classification requires that subjects meet fatigue severity criteria and exhibit four of eight other symptoms, but it does not include specific neurocognitive, cardiorespiratory, or thermoregulatory impairments required in the ICC criteria. Accordingly, the ICC is more selective for ME/CFS patients than the Fukuda definition.

Several brain magnetic resonance imaging (MRI) techniques used in ME/CFS patients demonstrated decreased global and regional grey and white matter volumes, increased T1-weighted and T2-weighted signal intensity, and higher signal intensity in white matter and basal ganglia regions. Single-photon emission computed tomography (SPECT) revealed a decreased regional cerebral blood flow, while positron emission tomography (PET) detected neuroinflammation. Blood oxygen level-dependent (BOLD) demonstrated impaired connectivity within the brainstem and decreased functional connectivity in primary cognitive networks. Nonetheless, neuroimaging techniques did not yield a comprehensive pathophysiological comprehension of ME/CFS.

DTI is an advanced MRI modality that uses the Brownian motion of water molecules to provide information about the structure of axons and their myelin sheaths. DTI enables the visualization of neural pathways and connectivity. During the processing of DTI data, multiple parameters are estimated, including fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD), radial diffusivity (RD) and mode of anisotropy (MO). Because the main advantage of DTI over conventional structural MRI is its sensitivity to tissue microstructure, DTI has been used to study white matter integrity, axonal damage, and myelin loss in neurodegenerative diseases. The authors noted that a limited number of studies have utilized brain diffusion tensor imaging in ME/CFS to examine microstructural changes in brain tissue. One study showed increased fractional anisotropy values in the right arcuate fasciculus, and the second study reported decreased fractional anisotropy values in the genu of the corpus callosum and the right anterior limb of the internal capsule in ME/CFS patients.



About the study

The study enrolled 25 patients diagnosed with ME/CFS who met Fukuda criteria (ME/CFS_{Fukuda}), 18 ME/CFS patients who met ICC criteria (ME/CFS_{ICC}), and 26 healthy control subjects without exclusionary medical disorder.

The authors also performed voxel-based DTI parameter regression by incorporating clinical measures as follows: the 36-item health survey questionnaire (SF36), the SF36 physical and mental scores, information processing score (Procinfo) a sleep disturbance score (SDS), heart rate (HR), heart rate variability (HRV), respiratory rate, and cognitive Stroop color-word test.

Results

For seven DTI parameters, a group comparison between 25 ME/CFS_{Fukuda} patients and 26 healthy controls found no statistically significant cluster, and patients diagnosed with ME/CFS_{Fukuda} were excluded from further analysis.

A group comparison of ME/CFS_{ICC} and healthy controls showed significant differences in the brainstem and superior longitudinal fasciculus region. Significant clusters exhibiting decreased axial diffusivity and mean diffusivity were formed in the descending cortico-cerebellar tract in the midbrain and pons. This demonstrates diffusion deficits in the frontopontine tract within the midbrain, and extending to crossing fibers of the pontine nuclei, involved in the motor activities *via* the cerebellum.

The DTI parameters, such as axial diffusivity, mean diffusivity and radial diffusivity were found to form significant clusters in the hippocampus and parahippocampal gyrus. Both mean and radial diffusivity showed a significant cluster in the corpus callosum, posterior cingulate, and Brodmann area-36. The mean diffusivity also formed a cluster within the external capsule. The authors have noted that the observed deficits in axial diffusivity may be related to impairment of central motor control and preparation for motor response in some motor tasks, as previously reported in some ME/CFS patients.

The cluster of the superior longitudinal fasciculus, which is involved in processes such as attention, memory, emotions, and language, exhibited a significantly decreased mode of anisotropy. According to the authors, the observed impairments of the brainstem and superior longitudinal fasciculus may underlie some of the core affective symptoms reported in ME/CFS patients.

A voxel-based DTI parameter regression demonstrated that fractional anisotropy in both grey and white matter regions showed abnormal regressions with clinical measures, such as the information processing score (Procinfo), the SF36 physical, the sleep disturbance score, and the respiration rate. The DTI parameters axial diffusivity, mean diffusivity and radial diffusivity showed abnormal regression with Procinfo clusters in the hippocampus and parahippocampal gyrus, which are involved in encoding memories and processing different types of stimuli. Fractional anisotropy *versus* sleep disturbance score showed a significant cluster in Brodmann area-44. The mean diffusivity and radial diffusivity *versus* respiration rate revealed significant clusters in Brodmann area-9.

Conclusion

This study demonstrated that DTI parameters are sensitive to microstructural changes in patients diagnosed with ME/CFS_{ICC}, particularly in the brainstem.

The authors emphasized that this investigation needed a stricter ICC definition of ME/CFS to identify ME/CFS neuropathology because there were no significant differences in DTI parameters between the more broadly classified ME/CFS_{Fukuda} and healthy control subjects.

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