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Editors Welcome

Silent symptoms of multiple sclerosis

Despite a significant conversion rate of "radiological isolated syndrome" to multiple sclerosis, recent recommendations favour watchful waiting (Lebrun, 2015). A "prodromal phase" of multiple sclerosis is now considered. Wijnand et al. (2019) documented increased hospital and physician contacts 5 years prior to onset of MS when compared to healthy controls. Both these so called "preclinical" (or better "prediagnostic") stages lack assessments of the most common complaints: cognitive impairment, fatigue, depression and anxiety (Ribbons et al., 2017; Pakpoor et al., 2018). These disorders, although now readily accepted as part of the symptom spectrum of MS, are often not monitored despite being leading causes of exclusion from the workforce (Povolo et al., 2019). If we included these "silent symptoms" in our clinical assessment we would likely be able to diagnose MS closer to its actual onset and therefore have a better impact on disease course and long-term disability (Giovannoni G, 2017).

The recent increase in predominantly descriptive research on MS fatigue probably results from integrating patient into research planning. Patient advocacy groups clearly outline this symptom as the most debilitating and for which therapeutic options are limited. In this month's issue of MSARD 3 articles focus on fatigue. The MUSICADO group published a cross-sectional study on their paediatric onset MS patients (n = 106) compared to 210 matched healthy controls. There were significant differences in fatigue, depression and quality of life between the two groups but not in social interaction. This indicates that potential isolation due to the diagnosis of MS is not the reason for increased fatigue, QoL and depression scores (Storm van Gravesande et al., 2019). One study of 136 patients confirmed that (unsurprisingly) fatigue scores increase during relapse when compared to a group of MS patients attending a rehabilitation centre. The authors found a correlation of fatigue scores with autonomic dysfunction and suggest this may be explained by a neuroinflammatory reflex via the vagal nerve (Hanken et al., 2019). On the basis of similarity with sickness behaviour during viral infection or radiotherapy, it was initially assumed that fatigue correlates with inflammation. In fact, it often accompanies relapses and disease activity as shown by Hanken et al. (2019). In a small study, the proinflammatory cytokine TNF alpha correlated with fatigue (Flachenecker et al., 2004) although further investigations have failed to confirm this (Akcali et al., 2017). One critical argument was always that brain inflammation might not be identified easily using peripheral blood. The current issue's contribution from a Swedish group tries to clarify this by examining 38 early onset MS patients compared to 21 healthy controls. They measured inflammatory cytokines previously reported to be associated with MS activity (IL-1β, IL-6, CXCL1, CXCL10, CXCL13, CCL-22) in plasma and CSF. Although fatigue scores correlated well with depression and quality of life responses on questionnaires, they failed to correlate with inflammatory markers or other markers of disease severity like NfL, MRI lesion load or brain atrophy (Hansson et al., 2019). On the other hand, a longitudinal study of 122 MS patients clearly showed a correlation between annual averaged serum NfL with fatigue scores more so than SDMT or EDSS (Chitnis et al., 2018).

These reports highlight the difficulties in studying fatigue. Despite multiple investigations trying to identify an anatomical correlate, none has consistently been identified by conventional MRI techniques like lesion load, number of enhancing plaques or global brain atrophy (Palotai, 2019).

There could be several possible explanations for the lack of pathophysiological correlate:

1) Our definitions of MS fatigue are not specific enough.

Patients may in fact experience fatigue related to lack of sleep or concurrent medications, and they may have different biomarker characteristics than patients with isolated fatigue with no better explanation than MS.

2) Our outcome measures of fatigue are flawed.

By definition, fatigue quantification relies on self-report surveys. The fatigue severity score (FSS) predominantly addresses physical fatigue and neglects the more dominant cognitive fatigue present in younger less disabled patients. The Modified Fatigue Impact Scale (MFIS), developed by the National MS Society (USA), was adapted from the Fatigue Impact Scale for MS patients based on interviews relating to the impact of fatigue on their lives. This questionnaire assesses physical, cognitive and psychosocial functioning. Separation in these subcategories is often neglected. In keeping with most questionnaires, it is subjective and measures perceived difficulties with specific tasks or activities. It is therefore not surprising that it correlates with depression as fatigue is a common symptom of depression. Even some questions used to assess depression for example, overlap with those used in fatigue scores.

3) We think too simplistically

We need to look more into neuronal circuits as in mental health disorders (Williams, 2016; Underwood, 2019). The descriptive diagnosis of depression and anxiety is currently under question since advanced MRI techniques have demonstrated distinct circuit dysfunctions subdividing the simplistic DSM criteria into specific circuit dysfunction. Does fatigue imply a decreased level of alertness and is related to the orexin system via the hypothalamic axis? Or is it related to lack of excitatory axons and imbalance between neurotransmitters? An early study from 1997 (Roelcke et al.) already recognised with PET imaging that dysfunction in the prefrontal and thalamic regions leads to fatigue.

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Any lesion disrupting the cortico-striato-thalamo-cortical circuit via glutaminergic or dopaminergic pathways can potentially result in fatigue (Arm et al., 2019). Advanced MRI techniques, like diffusion tensor imaging have for example demonstrated associations between fatigue levels and lower fractional anisotropy (FA) indicating axonal dysfunction in the right temporal cortex (Bernitsas, 2017). Magnetic resonance spectroscopy has also been able to correlate fatigue scores with decreased N-Acetyl Aspartate again associating this symptom with axonal loss (Tartaglia et al., 2004).

There remains a desperate need for an objective outcome measure for fatigue in order to prevent this symptom from occurring or to develop effective therapies.

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