Do isolated cognitive relapses exist? Commentary

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Cognitive impairment is frequent in patients with multiple sclerosis (PwMS). The cognitive deficits could worsen along the disease contributing to significant disability taking into account some heterogeneity among PwMS. However, the possibility of acute cognitive change has been reported during relapse, which includes physical symptoms, with full or partial recovery.[1–3] Besides, the concept proposed by Pardini et al.[4] relating to 'Isolated Cognitive Relapses' (ICRs) – with no physical worsening – based on a transient decrease of the Symbol Digit Modalities Test (SDMT) in PwMS is debated. The SDMT assessing mainly information processing speed has been well validated in MS, and its clinically meaningful change has been proposed based on ecological endpoint.[5] Nevertheless, Pardini et al.[4] acknowledged some limitations concerning the choice of this definition of ICRs only based on one neuropsychological (NP) assessment. They underlined that ICRs were not self-identified, but they highlighted the value of informant versions of the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ).[6] Interestingly, Pardini et al.[4] also supported the clinical relevance of ICRs due to their association with cognitive daily functioning and further cognitive decline in PwMS.

Besides, Baldwin et al.[7] emphasized that the data published by Pardini et al.[4] came from retrospective study with a small sample size. In fact, it could be unjustly concluded that ICRs do not exist, whereas they are simply under-recognized by both patients and physicians. Indeed, one could also wonder whether neurologists use some tools for identifying ICRs in practice. Importantly, baseline and follow-up relevant cognitive assessments are needed to be able to detect prospectively ICRs in clinical setting.

Moreover, cognitive impairment is driven by the cumulative brain inflammation and the ongoing neurodegeneration. It is questionable concerning the mechanisms leading to ICRs. The occurrence of new MS lesions in key and relevant areas involved in cognitive functions has been proposed for supporting them.[4] One could argue that the presence of active inflammation could also alter the efficiency of brain networks and synaptic functioning that could drive a decrease of acute cognitive performance.[8] The presence of gadolinium enhancing (Gd+) lesion is part of the definition of disease activity in MS, and has been used for supporting cognitive relapse.[4,9] But the presence of Gd+ lesions only means the breakdown of blood–brain barrier, and does not reflect all types of inflammation within the brain. Most of the new grey matter lesions relevant for cognition are not identified, as well as diffuse inflammation and microglial activation that are not visualized with conventional imaging.

So as defended by Baldwin, no large data could support the attractive concept of ICRs. Further longitudinal studies are required to confirm the presence and the relevance of ICRs in PwMS. This controversy underlines the absence of consensual definition of cognitive relapse, and highlights the importance of regular cognitive evaluations from the diagnosis of MS to the follow-up visits in clinical practice. These findings could help to disentangle this important question in the future, which could have prognostic and therapeutic implications for PwMS.

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