MRI techniques and cognitive impairment in the early phase of relapsing-remitting multiple sclerosis

Abstract  Correlation studies between various conventional and non-conventional MRI parameters and cognitive impairment in the early stages of multiple sclerosis (MS) are lacking, although it is known that a number of patients with early MS have mild cognitive impairment. Our aim was to explore whether this cognitive impairment is dependent on the extent and severity of the burden of disease, diffuse microscopic brain damage or both. We studied 63 patients with clinically definite relapsing-remitting (RR) MS, duration of disease 1–10 years and Expanded disability status scale scores ≤ 5.0. Mean age was 35.4 years, mean duration of disease 5.8 years and median EDSS score 1.5. Neuropsychological performance, psychological function, neurological impairment and disability were assessed. The patients also underwent MRI, including magnetisation-transfer (MT) studies. We quantified the lesion load on T2- and T1-weighted images, the magnetisation transfer ratio (MTR) of normal-appearing brain tissue (NABT) and the brain parenchymal fraction (BPF). No significant difference was found between lesion loads in patients with and without cognitive impairment. In 15 patients (23.8%) with overall cognitive impairment, median BPF and average NABT MTR were significantly lower than those in patients without cognitive impairment (0.868 vs 0.892, P = 0.02 and 28.3 vs 29.7 P = 0.046, respectively). Multiple regression analysis models demonstrated that the only variables independently correlated with cognitive impairment were: BPF (R = 0.89, P = 0.001) and average NABT MTR (R = 0.76, P = 0.012). Our findings support the hypothesis that, cognitive decline in patients with MS, a low disability score and short duration of disease is directly associated with the extent and severity of diffuse brain damage. The loss of brain parenchyma did not correlate with the severity of microscopic damage in the NABT, indicating that the two processes could be distinct in the early stages of the disease.

Keywords  Multiple sclerosis · Cognition · Brain atrophy · Magnetic resonance imaging · Magnetisation transfer

Introduction  Considerable progress has been made in the study of the correlation between cognitive deficits and the extent and location of abnormalities seen on MRI techniques in patients with multiple sclerosis (MS). Conventional (proton-density (PD)/T2-weighted image lesion load) [1, 2, 3, 4, 5, 6] and non-conventional (T1-weighted image lesion load, brain atrophy, magnetisation transfer imaging (MTI) and magnetic resonance spectroscopy
Almost all correlation studies between abnormalities on MRI and patterns of cognitive impairment have been performed on patients with a long duration of disease, mild or severe disability, and mixed types of disease course [5, 6, 10, 11]. They are weakened by clinical heterogeneity and by the fact that the results are not reported in relation to the disease course, although it has been demonstrated that patients with relapsing-remitting (RR) and primary progressive (PP) have less relevant cognitive decline than those with secondary progressive (SP) disease [5, 7, 10, 19, 20, 21]. The majority of trials enrol patients with RR-MS, and Expanded disability status scale (EDSS) score of 0–5.0, a short duration of disease (< 10 years), aged 18–60 years. Cognitive disturbances is more frequent in patients with a longer duration of disease [22, 23], although a number of patients in the early phase of MS have impairment of various cognitive domains, with an evident impact on everyday activities and social function [24, 26].

MRI and pathological studies of the early stage of the disease have shown that widespread abnormalities can develop in the brain parenchyma outside macroscopic lesions of multiple sclerosis [27, 28, 29, 30, 31, 32, 33, 34] and that this diffuse brain damage is probably responsible in part for the physical disability in the early phase. It can be hypothesised that cognitive impairment in the early phase may be due not only to the extent and severity of the burden of the disease but also to the severity of microscopic changes in the NABT. Recent studies of heterogeneous cohorts of patient with a long duration of disease and high disability scores support this hypothesis [9, 10, 11, 12, 13, 35]. They also confirmed, in agreement with PET studies [16, 36, 37], that the severity of changes within the lesions of MS and quantitative assessment of the extent and severity of the pathological process in the brain are relevant to cognitive decline, suggesting that widespread damage of the brain could be a factor in functional disconnection of various cortical and subcortical regions [8, 38].

The challenge is to find answers to questions about cognitive impairment in early RR-MS, such as which conventional or non-conventional MRI marker correlates best with cognitive impairment, and whether cognitive impairment is related more to the extent and severity of the burden of disease, microscopic diffuse brain damage, or both. In an attempt to answer to these questions we performed an extensive analysis adopting the principal inclusion criteria of recent clinical trials in RR-MS. The study was designed to explore the possible correlation between the extent and severity of the burden disease (lesion load on T2- and T1-weighted images), average lesion magnetisation transfer ratio (MTR), microscopic diffuse brain damage (brain parenchymal fraction and MT histograms of the NABT) and overall cognitive impairment.

Material and methods

We studies 63 consecutive unselected patients with definite RR-MS according to the criteria of Poser et al. [39]. Patients being seen for routine follow-up, or for problems unrelated to cognitive disturbance or exacerbations of disease, and those admitted to hospital for examinations were asked to participate in the study.

Before complete neuropsychological assessment, we carried out two tests, the Mini-mental state examination (MMSE) [40] and Standard Raven progressive matrices (SRPM) [41] adjusted for age, sex and educational levels, to assess attention and compliance with the proposed battery of tests. We chose a cut-off value: ≥ 24 for the MMSE and the 15th percentile for SPRM. Inclusion criteria were: definite MS, with an RR course, age 18–60 years, duration of disease 1–10 years, EDSS score ≤ 5.0 [42], and written informed consent. Exclusion criteria were concomitant disorders (cerebrovascular disease, neurodegenerative disorder, a history of alcohol abuse, severe visual deficit or severe arm weakness) and/ or pre-existing psychiatric or psychological disorders which can cause cognitive impairment or preclude completion of the cognitive tests; a current exacerbation of the disease; and immunomodulating and/or steroid and/or psychoactive drugs treatment in the 3 months preceding the study. Some of these exclusion criteria arise from our decision to follow the common clinical inclusion criteria for trials in RR-MS and the fact that all patients were screened with the MMSE and SPRM to check their attention and compliance. For these reasons our data do not represent the real prevalence of cognitive disturbance in patients overall with RR-MS.

A neurologist (R.Z.) specialised in MS care classified patients as having RR-MS according to recently published criteria [43] (i.e., clearly defined disease relapses with either full recovery or sequelae, but without disease progression between the relapses). All patients had a neurological examination. Neurological impairment, disability and independence were assessed using the EDSS and the Functional independence measure (FIM) [44].

Within 48 h of the MRI examination, an extensive battery of neuropsychological tests were administered, including measures of attention/concentration/information processing speed, memory, abstract/conceptual reasoning, language, visual and perceptual skills and verbal intelligence. We specifically chose tests that do not require fine visual acuity or motor speed/dexterity. The attention/concentration/information processing speed was assessed by means of the Paced auditory serial addition test (PASAT) [45], the Stroop colour word interference test [46] and the verbal fluency subset of the revised Wechsler adult intelligence scale (WAIS-R) [47]. Memory was evaluated by the two subsets of the WAIS-R: digit span forward and feedback and by the story recall sublist of the bilingual aphasia test (BART) [48]. Abstract/conceptual reasoning skills were tested by the SRPM. The linguistic parameters chosen were: syntactic comprehension of mistakes, semantic mistakes, syntactical and morphological mistakes. The numbers of verbal paraphasias, neologisms and agrammatisms as a measure