Neurol Sci (2010) 31 (Suppl 2):S245–S248
DOI 10.1007/s10072-010-0370-x

Cognition in multiple sclerosis: relevance of lesions, brain atrophy and proton MR spectroscopy

Antonio Giorgio · Nicola De Stefano

Published online: 16 July 2010
© Springer-Verlag 2010

Abstract The overall burden of brain MRI-visible lesions does not fully account for cognitive impairment in multiple sclerosis (MS). Several MRI studies have highlighted the importance of brain damage in the normal-appearing brain tissue. Brain atrophy (global, cortical, white and deep grey matter) is related to cognitive deficits in MS patients and this holds true since the earliest disease stages. Non-conventional MRI techniques such as proton MR spectroscopy have related metabolic changes in specific brain areas to specific cognitive deficits. Overall, data provided by MRI support the notion that cognitive disturbances need to be considered for a more complete clinical characterisation of patients with MS, including those with "benign" MS.

Keywords MRI · Cognition · Brain atrophy · MR spectroscopy

Introduction

Cognitive impairment is an important cause of disability in people with multiple sclerosis (MS), resulting in a significant functional impairment during daily activities, sometimes despite minimal physical disability. It occurs in about 40–65% of MS patients, affecting most frequently cognitive domains such as memory, attention, speed of information processing and executive functions.

Cognitive impairment is not only present in the established forms of MS but it has also been shown in patients with clinically isolated syndromes (CIS) suggestive of MS or newly diagnosed MS [1]. The lack of significant correlation generally found between cognitive scores and MRI measures of disease severity in these types of MS suggests that cognitive impairment may predate the appearance of gross structural abnormalities on MRI and thus serve as an early marker of disease activity in MS. By contrast, a different study on CIS patients found that performance on paced auditory serial addition test (PASAT), a comprehensive measure of cognitive status and a reference task for cognitive assessment of MS patients, was explained by several structural and functional imaging components [2]. The preservation of cognitive function has been recently proposed as an important requisite to reliably define patients with the so-called "benign" MS (B-MS), i.e., patients who are fully functional several years after disease onset [3].

Traditionally, imaging studies investigating the relationship between cognition and brain pathology in MS have focused their attention on the effects of lesions and atrophy, which are measured through conventional MRI.

More recently, novel imaging techniques such as magnetisation transfer imaging (MTI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS) have provided further insights into the understanding of cognitive impairment in people with MS, highlighting the importance of the subtle damage in the normal-appearing brain tissue (NABT) which goes undetected by conventional imaging.

Lesions

Since early imaging studies, cognitive impairment was reported more frequently in relapsing–remitting (RR) MS patients with higher lesion load than in those with lower

A. Giorgio · N. De Stefano (✉)
Quantitative Neuroimaging Lab,
Department of Neurological and Behavioural Sciences,
University of Siena, Viale Bracci 2, 53100 Siena, Italy
e-mail: destefano@unisi.it

lesion load. This has been demonstrated not only for white matter (WM) lesions but also for cortical/subcortical lesions. Further, in B-MS patients both T2 and T1 lesion load were higher in cognitively impaired than in cognitively preserved patients [4]. More recently, a better in vivo detection of cortical lesions (CLs) in MS patients has been made possible by using novel MRI sequences such as double inversion recovery (DIR). These studies showed that CLs were predictive of cognitive impairment scores in patients with RR MS.

Moderate-to-strong correlations have been reported between scores of cognitive performance and lesion load. In particular, total lesion area represented a robust predictor for different measures of cognitive status such as recent memory, abstract/conceptual reasoning, language and visuospatial problem solving [5, 6]. A pivotal study of interferon (IFN) beta-1b showed that baseline T2 lesion load predicted cognitive performance scores 16 years later. Neuropsychological test scores, together with T1-hypointense lesion load and male gender turned out to be the only predictors able to identify those B-MS patients entering a progressive course of disease after a mean follow-up of 5 years [7].

Some studies have also demonstrated that analysis of regional cerebral lesion load may assist in understanding the pattern and course of cognitive decline in MS. In fact, higher WM lesion load in the frontal lobe has been linked to frontal lobe deficits and to worse performance on a standard conceptual reasoning task (Wisconsin Card Sorting Test). Further, lesions in the left frontal lobe best predicted impaired abstract problem solving, memory and word fluency whereas lesions in the left parieto-occipital lobe were able to predict deficits in verbal learning and complex visual-integrative skills [6].

Overall, the relationship between cognitive impairment and lesion load is moderate, suggesting that cognitive dysfunction in MS has a complex and multifactorial etiology which is not adequately explained by pathological features captured by conventional MRI.

Brain atrophy

Brain atrophy is present from the earliest stages of MS, particularly in the neocortex [8] and proceeds relentlessly throughout the course of disease at a rate that seems largely independent of the MS subtype [9]. Brain atrophy measurements have been particularly useful in furthering our understanding on the relationship between brain structure and cognition in MS. Both GM and WM atrophy are clinically relevant for cognitive impairment, being related to deficits of specific cognitive domains.

Early imaging studies already showed that scores of neuropsychological tests were significantly lower in patients with larger third ventricle, severe enlargement of lateral ventricles and widening of cortical sulci. Size of the corpus callosum appears to be relevant to cognition in people with MS. In fact, atrophy of the whole corpus callosum predicted test performance on measures of mental processing speed and rapid problem solving [10], whereas atrophy of the anterior callosum strongly affected the performance on verbal fluency task. In addition, performance on tasks exploring interhemispheric transfer of different information modalities (auditory, sensory and motor) was associated with atrophy in different parts of the corpus callosum, suggesting the potential clinical values of callosal involvement and the usefulness of MS as a model of interhemispheric disconnection.

More recently, measures of central (width of third ventricle) and whole brain (brain parenchymal fraction) atrophy were shown to account for more variance in MS cognition than lesion load. In particular, the width of the third ventricle seems to have a role in predicting cognitive impairment in patients with MS, distinguishing secondary progressive from RR courses [11] and displays, among different MR markers, the highest correlation with cognition, accounting for almost half the variance in the overall cognitive performance [12].

Neocortical volume loss was found in cognitively impaired but not in cognitively preserved MS patients, including B-MS [4], and this was significantly correlated with a poorer performance on tests of verbal fluency, attention/concentration and verbal fluency [13]. Further, in a group of mildly disabled MS patients' performance on the PASAT was associated with global GM volume as well as with GM volume in regions involved with working memory and executive function such as bilateral prefrontal cortex, precentral gyrus, superior parietal cortex and right cerebellum. In the same study, patients with low cognitive performance showed, compared to their demographically matched control subjects, more extensive and bilateral volume reductions in the frontal, temporal and parietal lobes.

It was also shown that, after controlling for third ventricle width, there exists a significant correlation between neuropsychological tests and GM volume obtained from specific regions within the prefrontal cortex [14]. In addition, left frontal atrophy was associated with tests of auditory/verbal memory while right frontal atrophy was associated with impairment in visual episodic and working memory.

Deep GM of the brain is another relevant site for cognitive status in people with MS. Thalamic atrophy was moderately-to-strongly correlated with performance in multiple cognitive domains, thus showing to be a reliable predictor of cognitive impairment in MS [15]. Volume loss in the hippocampus, a structure of the archicortex which is

critical for memory functions, and its subregions, was related to worsening performance on word-list learning, a task requiring memory encoding, but not to performance on the PASAT, a test of information processing speed [16].

An important contribution stems from longitudinal MRI studies, which have shown that changes in cognitive status and measures of brain atrophy rate are highly correlated. The rate of global brain atrophy early in the MS course accounted for a significant variance in the overall cognitive performance and, more specifically, in memory and attention/speed of information processing 5 years later [17], suggesting that imaging performed early in the disease is able to predict later cognitive impairment. Increase in neocortical volume loss was higher in deteriorating than in stable or improving MS patients after 2.5 years of follow-up [18]. The same study showed that neocortical volume change was correlated with performance in a verbal fluency test such as the Word List Generation test.

Several attempts have been made for a symptomatic treatment of cognitive impairment using pharmacological agents and a few studies have investigated the effects of a cognitive training and its relationship with MRI features, particularly with brain atrophy. In a recent study of this type [19], a 6-week home-based cognitive training programme for memory functions led to an improvement of functions such as verbal learning, verbal memory and working memory. In addition, the impact of treatment on performances of verbal memory was independent from brain atrophy, whereas brain atrophy did play a significant role for the other memory functions.

Proton MR spectroscopy

Among non-conventional MRI techniques, MRS, which provides measures of important metabolites within the brain [20], has shown a good sensitivity for cognitive status of people with MS, especially in the NABT, being able to distinguish MS patients with and without cognitive impairment. Ratios of *N*-acetyl aspartate (NAA), a putative marker of neuroaxonal integrity, to both creatine and choline displayed in sites of the right hemisphere a higher correlation with cognitive performance scores than in those of the left hemisphere [12]. A recent investigation of genotype–phenotype association in MS showed that human leucocyte antigen (HLA) DRB1*1501 allele is associated with a reduction in NAA within normal-appearing WM and to impairment of cognitive function as measured by the PASAT performance [21]. Moreover, in early-stage MS, spectroscopic axonal damage of the right locus ceruleus in the pons was related to selective attention deficit, as measured by a dichotic listening paradigm [22]. MRS has also been useful in revealing a link between frontal brain region and memory function in MS, by showing that NAA/Cr of the frontal cingulate gyrus is significantly related to distinct memory function, as measured by Wechsler Memory Scale.

Conclusions

Although cognitive status of people with MS is linked to both lesion load and brain atrophy, most of its variance still remains unexplained. This may be due to several factors. First, lesions provide a useful measure of focal macroscopic pathology, even though they lack pathological specificity due to their inability to discriminate between demyelination, axonal loss, inflammation, gliosis and edema. Second, MS-related brain damage is widespread, also affecting areas of the NABT, where microscopic pathology, in particular axonal loss, is not fully captured by conventional MRI. In this context, the application of non-conventional MRI techniques such as MRS has allowed to at least partially overcome these issues.

Conflict of interest The authors declare that they have no conflict of interest related to the publication of this article.

References

1. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, Houtchens MK, Sperling RA, Khoury SJ, Guttmann CR, Weiner HL (2007) Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler 13(8):1004–1010
2. Ranjeva JP, Audoin B, Au Duong MV, Confort-Gouny S, Malikova I, Viout P, Soulier E, Pelletier J, Cozzone PJ (2006) Structural and functional surrogates of cognitive impairment at the very early stage of multiple sclerosis. J Neurol Sci 245 (1–2):161–167
3. Rovaris M, Barkhof F, Calabrese M, De Stefano N, Fazekas F, Miller DH, Montalban X, Polman C, Rocca MA, Thompson AJ, Yousry TA, Filippi M (2009) MRI features of benign multiple sclerosis: toward a new definition of this disease phenotype. Neurology 72(19):1693–1701
4. Amato MP, Portaccio E, Stromillo ML, Goretti B, Zipoli V, Siracusa G, Battaglini M, Giorgio A, Bartolozzi ML, Guidi L, Sorbi S, Federico A, De Stefano N (2008) Cognitive assessment and quantitative magnetic resonance metrics can help to identify benign multiple sclerosis. Neurology 71(9):632–638
5. Rao SM, Leo GJ, Haughton VM, St Aubin-Faubert P, Bernardin L (1989) Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology 39 (2 Pt 1):161–166
6. Swirsky-Sacchetti T, Mitchell DR, Seward J, Gonzales C, Lublin F, Knobler R, Field HL (1992) Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis. Neurology 42(7):1291–1295
7. Portaccio E, Stromillo ML, Goretti B, Zipoli V, Siracusa G, Battaglini M, Giorgio A, Bartolozzi ML, Guidi L, Sorbi S, Federico A, Amato MP, De Stefano N (2009) Neuropsychological and MRI measures predict short-term evolution in benign multiple sclerosis. Neurology 73(7):498–503

8. De Stefano N, Matthews PM, Filippi M, Agosta F, De Luca M, Bartolozzi ML, Guidi L, Ghezzi A, Montanari E, Cifelli A, Federico A, Smith SM (2003) Evidence of early cortical atrophy in MS: relevance to white matter changes and disability. Neurology 60(7):1157–1162
9. De Stefano N, Giorgio A, Battaglini M, Rovaris M, Sormani MP, Barkhof F, Korteweg T, Enzinger C, Fazekas F, Calabrese M, Dinacci D, Tedeschi G, Gass A, Montalban X, Rovira A, Thompson A, Comi G, Miller D, Filippi M (2010) Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. Neurology 74(23):1868–1876
10. Rao SM, Bernardin L, Leo GJ, Ellington L, Ryan SB, Burg LS (1989) Cerebral disconnection in multiple sclerosis. Relationship to atrophy of the corpus callosum. Arch Neurol 46(8):918–920
11. Benedict RH, Bruce JM, Dwyer MG, Abdelrahman N, Hussein S, Weinstock-Guttman B, Garg N, Munschauer F, Zivadinov R (2006) Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. Arch Neurol 63(9):1301–1306
12. Christodoulou C, Krupp LB, Liang Z, Huang W, Melville P, Roque C, Scherl WF, Morgan T, MacAllister WS, Li L, Tudorica LA, Li X, Roche P, Peyster R (2003) Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. Neurology 60(11):1793–1798
13. Amato MP, Bartolozzi ML, Zipoli V, Portaccio E, Mortilla M, Guidi L, Siracusa G, Sorbi S, Federico A, De Stefano N (2004) Neocortical volume decrease in relapsing–remitting MS patients with mild cognitive impairment. Neurology 63(1):89–93
14. Tekok-Kilic A, Benedict RH, Weinstock-Guttman B, Dwyer MG, Carone D, Srinivasaraghavan B, Yella V, Abdelrahman N, Munschauer F, Bakshi R, Zivadinov R (2007) Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. Neuroimage 36(4):1294–1300
15. Houtchens MK, Benedict RH, Killiany R, Sharma J, Jaisani Z, Singh B, Weinstock-Guttman B, Guttmann CR, Bakshi R (2007) Thalamic atrophy and cognition in multiple sclerosis. Neurology 69(12):1213–1223
16. Sicotte NL, Kern KC, Giesser BS, Arshanapalli A, Schultz A, Montag M, Wang H, Bookheimer SY (2008) Regional hippocampal atrophy in multiple sclerosis. Brain 131(Pt 4):1134–1141
17. Summers M, Fisniku L, Anderson V, Miller D, Cipolotti L, Ron M (2008) Cognitive impairment in relapsing–remitting multiple sclerosis can be predicted by imaging performed several years earlier. Mult Scler 14(2):197–204
18. Amato MP, Portaccio E, Goretti B, Zipoli V, Battaglini M, Bartolozzi ML, Stromillo ML, Guidi L, Siracusa G, Sorbi S, Federico A, De Stefano N (2007) Association of neocortical volume changes with cognitive deterioration in relapsing–remitting multiple sclerosis. Arch Neurol 64(8):1157–1161
19. Hildebrandt H, Lanz M, Hahn HK, Hoffmann E, Schwarze B, Schwendemann G, Kraus JA (2007) Cognitive training in MS: effects and relation to brain atrophy. Restor Neurol Neurosci 25(1):33–43
20. De Stefano N, Filippi M (2007) MR spectroscopy in multiple sclerosis. J Neuroimaging 17 Suppl(1):31S–35S
21. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, Hauser SL, Pelletier D (2009) Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 72(9):800–805
22. Gadea M, Martinez-Bisbal MC, Marti-Bonmati L, Espert R, Casanova B, Coret F, Celda B (2004) Spectroscopic axonal damage of the right locus coeruleus relates to selective attention impairment in early stage relapsing–remitting multiple sclerosis. Brain 127(Pt 1):89–98