

Does multiple sclerosis cause progressive and widespread cognitive decline?

Marina Katsari¹, Dimitrios Kasselimis^{1,2}, Georgios Koutsis³, and Constantin Potagas¹

¹Neuropsychology and Language Disorders Unit, 1st Department of Neurology, Eginition Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece

²Division of Psychiatry and Behavioral Sciences, School of Medicine, University of Crete, Heraklion, Greece.

³Neurogenetics Unit, 1st Department of Neurology, Eginition Hospital, School of Medicine, National and Kapodistrian University of Athens, Greece

Abstract

The existence of cognitive deficits in Multiple Sclerosis (MS) can be supported by clinical observation and assessment or large-scale research studies. The fact that part of the MS patient population does demonstrate some type of cognitive impairment may be unequivocal, although a crucial question remains: Is this impairment in the context of a progressive decline? The literature provides inconclusive evidence. Nevertheless, the notion of “MS dementia” seems to be gaining popularity during the last decade. In this short review, we present the findings of the main longitudinal studies on cognitive course of MS patients in an attempt to reveal the vulnerabilities of that particular view. Overall, we corroborate the idea that MS does not inevitably result in cognitive decline with advancing age, and further argue that researchers and clinicians should take the emerging trend of “MS Dementia” with a grain of salt.

Keywords: Multiple Sclerosis; longitudinal studies; cognitive decline; dementia

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The cognitive deficits in MS, and their progression over time

Multiple Sclerosis (MS) is a chronic, immune-mediated neurological disease of the central nervous system, which typically causes damage to myelin sheaths and secondary axonal loss. In time, accumulating widespread lesions in the central nervous system may cause problems associated with motor control and sensation, as well as fatigue, depression, and cognitive deficits. [1]. The reported prevalence of cognitive deficits in MS patients ranges from 20 to 65% [2]. This rather wide range could be attributed to several methodological factors, since most relevant studies differ in terms of the definition of cognitive impairment, the inclusion criteria, and the neuropsychological tests used. This limitation notwithstanding, one can clearly see a trend emerging from these studies: information processing speed [3-5], complex attention [6,7], and long-term memory [8-10] seem to be the cognitive functions most affected in MS.

Regarding the cognitive course of MS, it has been argued that progression of the disease parallels a continuously deteriorating cognitive status, characterized as “subcortical dementia” [10], or “white matter dementia” [11]. However, the term “dementia” implies that the nature of the observed deficits is progressive, therefore suggesting a decline rather than an isolated impairment in specific cognitive domains. Mahler and Benson [12] (cited in Rao, 1990, pp. 95-96), in their attempt to resolve this issue, proposed that the term cognitive dysfunction might be used when deficits involve only one or two areas; more extensive dysfunction deserving the term dementia. It should be noted, however, that the aforementioned definition, does not take into account one of the most crucial criteria for dementia, namely every-day living functionality. Benedict & Bobholz [13], in a study investigating this topic, indicated that only 22% of their sample truly met the criteria for dementia, according to DSM (American Psychiatric Association, V) [14] or ICD10 [15]. Moreover, a detailed examination of longitudinal studies focusing on the cognitive course of MS patients, reveals that cognitive deterioration, far from being the norm, is usually restricted to specific domains [3,11,16-29]. More specifically, deterioration is shown in only a small proportion (and is usually restricted to

specific cognitive domains) in most longitudinal studies of cognition in MS. Additionally, such findings are often contradictory, and therefore a definitive conclusion about which cognitive domains tend to decline over time cannot yet be drawn. The interpretation of such studies is further complicated, by the as-yet obscure effect of MS-related clinical factors on cognition. For example, physical disability, as measured by the Expanded Disability Status Scale (EDSS) appears to be associated with the severity of cognitive deficits in some studies [2,17,19,30]. In contrast, other studies show that only EDSS scores indicating severe disability (>4,5), are actually correlated with cognitive variables [3, 31,32]. As far as duration of illness is concerned, a recent cross-sectional study [2] showed that most patients started experiencing cognitive difficulties from the fifth year post onset. The subtype of MS has also been shown to affect cognition. In particular, patients with secondary progressive MS (SPMS) have significantly worse cognitive performance than patients with relapsing-remitting MS (RRMS) or primary progressive MS (PPMS), even when controlling for physical disability [33,29]. In the following section, we provide a brief, critical presentation of longitudinal studies that focus on cognitive course of different MS subtypes.

Longitudinal studies focusing on different MS subtypes

Most longitudinal studies on RRMS patients have relatively short time intervals (≤ 5 years) between initial and final assessment [e.g. 11, 16-18,20,24,25,28,31-34], while only few have longer time intervals between two assessments (7 to 20 years) [2,3,19,21,22, 27]. The results from these studies are inconclusive: Many of them demonstrate cognitive deterioration in processing speed [3,19,28,29], some in visual learning and memory [19,22,28,35], and others in verbal learning and memory [19-21]. Almost all of the aforementioned studies indicate selective decline, i.e. deterioration in specific cognitive domains. It is also noteworthy that that four of them did not show any significant cognitive deterioration over time [16,24,34,36].

Overall, only three of the above studies have fairly long time periods between the initial assessment and follow up (from 10

to 20 years) [19, 27,29], thus providing more robust findings. Two of them (10 and 18 years follow up, respectively), have partly converging results: Schwid et al.[27] found mild deterioration only in processing speed, and a small increase (5%) in the proportion of cognitively impaired patients over time. Strober et al. [29] found, in addition to a mild deterioration in processing speed, deteriorations in simple and complex auditory attention span, visual construction and episodic memory. In this study, the proportional increase in cognitively impaired patients over time was higher (18%). Interestingly, Schwid and colleagues [27] noted that patients with better baseline performance demonstrated greatest decline over time than patients cognitively impaired at baseline, while Strober et al. [29] suggested the same schema only for the SDMT test. Amato and colleagues [19] found significant decline in almost all cognitive domains between baseline and follow-up assessment (ten years interval). At baseline, the patient group showed impaired mean performance on verbal memory and abstract reasoning. Four years later, working memory difficulties emerged, and, after an additional period of 6 years, short term verbal and spatial memory impairments were evident. Furthermore, of the initially 37 cognitively unimpaired patients, only 20 remained as such, while the proportion of patients who became cognitively impaired at follow up, rose up to 56% (from 26%, at initial assessment). Nevertheless, there are some issues concerning this study, which should be addressed. Firstly, disease duration at baseline assessment was very short (mean: 1.5 years). Short disease duration at baseline assessment indicates that most patients may not yet have demonstrated cognitive dysfunction. As previously noted [2], cognitive decline is usually most clearly demonstrated beyond the fifth year of disease duration. . Furthermore, a more detailed examination of the cognitive grouping utilized, reveals an interesting observation. The proportion of mildly cognitive impaired patients is 8% at the 1st assessment, becomes 33% at 1st follow-up, and remains stable (34%) at the 2nd follow-up. The proportion of moderately cognitively impaired patients shows small fluctuations over time (18% , 16%, and 22% at first, second and third assessment respectively). The above percentages indicate that the number of mildly cognitive impaired patients may have increased 4 years post onset, however remained stable during the following 6

years. Furthermore, the proportion of the moderately impaired patients did not show significant increase, from onset to final assessment (4%). In sum, it seems that the number of patients who initially demonstrate cognitive deficits does not increase at a constant rate over time.

In the two longitudinal studies on PPMS patients [23,26], the time intervals are very short (two and three years respectively). Camp et al.[23] failed to find generalized cognitive decline. In particular, they found that, of the 73 patients that completed the Brief Repeatable Battery of Neuropsychological tests , 52 were intact at baseline (mean disease duration at baseline was 10, 4 years), and only 4 of them became impaired (using the definition of at least 3 tests scores below 1,5 SD). Patients who were mildly impaired at baseline (n=6) scored within normal range at follow-up, while 15 patients who were moderately to severely impaired at baseline remained stable. In this study, different versions of the neuropsychological battery were used, in order to avoid learning effects. Denney et al. [26] found that decline was restricted to processing speed, regardless of the initial cognitive status of the patients. It must be noted that the sample in this study was quite small, consisting of only 24 patients. A somewhat unexpected finding was that verbal memory showed significant improvement at follow up assessment for the whole sample. Due to the small time interval between the two assessments, this improvement could be attributed to learning effects, since, in contrast to the processing speed task, the verbal memory task is sensitive to learning effects. Finally, there is one study by Kujala et al.[18], which included a sample of mixed MS subtypes (relapsing-remitting and progressive) and implemented a quite short interval between assessments (3 years). The authors argue that 50% of the patients (22 out of 45) showed cognitive impairment already at baseline. This specific subgroup showed significant deterioration after 3 years, in verbal learning and memory, visuomotor performance, and processing speed. The rest of the patients remained cognitively intact at follow-up. In summary, the above short review does not support the notion of a definite, progressive, and widespread cognitive decline over time in MS.

Clinical and research implications

Dementia is a highly emotionally-charged word, which can have serious psychological implications on patients, who are usually young people, during the most productive period of their life, attending to be efficient in their job, and possibly trying to raise young children. Consequently, a clinician should be very cautious when interpreting the results of these studies, before he/she explicitly uses the term “dementia”, when treating an MS patient. It should be however made clear that the need for scepticism is not solely based on humanitarian reasons and the psychological status of the patient. It is rather a matter of a clinical consensus based on research evidence. We must acknowledge that results regarding the cognitive course of MS are still inconclusive and therefore the notion of “MS dementia” should be thoroughly scrutinized before becoming common ground. Otherwise, the belief of MS resulting in progressive cognitive decline, could lead to confirmation bias in future studies. We will briefly speculate on the reasons behind the above described blurry image and possible misconceptions, which could be attributed to methodological issues. First, the intervals adopted by different longitudinal studies vary dramatically, and are often too short. Judging from the available findings, we suggest that the time period between baseline and follow up, should be no less than 5 years, in order for possible cognitive changes to be detectable. Another methodological constraint of such longitudinal studies, is dropouts. Even though clinical, behavioural, and demographic variables (as measured at baseline) may not differ between the dropout group and the patient subsample assessed at follow-up in some studies, the fact that only part of the initial sample is re-assessed, may lead to distorted results. For example, it is possible patients with prominent mobility difficulties, who reportedly demonstrate greater cognitive impairment [3,31,32], may not visit the clinic for reassessment. If this limitation is not taken into consideration, any longitudinal study may be highly susceptible to statistical fallacies. It should be however noted that, by acknowledging this limitation, we do not suggest that the general outline emerging from the available findings can be attributed to statistical negligence or methodological misconduct. Another issue is the definition of impairment. The available studies may have different approaches with regard to

characterization of a patient as cognitively impaired, and may also use different psychometric tools for assessment. Finally, one should take into consideration possible differences stemming from the type of MS. For example, the prevalence of cognitive deficits is shown to be higher in secondary progressive MS subtype [30,33]. In addition, the course of the disease may manifest as a continuum with overlaps between types with advancing age (e.g. RRMS evolving into SPMS).

Conclusion

Cognitive course in MS is a rather complicated phenomenon, influenced by several factors, such as disability status, disease duration, MS subtype, type of assessment, time interval between assessments, manifestation of depression, and fatigue, among many others. Some of these factors are difficult to be controlled, in order to acquire clear and comprehensive results. Contradictory findings reported in the literature make clear that additional longitudinal studies are needed in order to elucidate the issue at hand. Thus far, there is no robust evidence allowing us to corroborate the idea of MS resulting in inevitable cognitive decline with advancing age. Therefore, we must remain sceptical against the emerging trend of “MS Dementia”.

References

1. Snyder, P. J., Nussbaum, P. D., & Robins, D. L. (2006). *Clinical neuropsychology: A pocket handbook for assessment*. American Psychological Association.
2. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie M, Bercovich E, Polliack M, Doniger GM, Stern Y, Khilkevich O, Menascu S, Hararai G, Gurevich M, Barak Y. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. *PloSone* 2013, 8(8), e71058
3. Bergendal, G., Fredrikson, S., & Almkvist, O. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *European Neurology* 2007, 57(4), 193-202. doi.org/10.1159/000099158

4. DeLuca J, Chelune GJ, Tulskey DS, Lengenfelder J, Chiaravalloti ND. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J Clin Exp Neuropsychol* 2004; 26: 550–62. DOI: 10.1080/13803390490496641
5. Janculjak D, Mubrin A, Brinar V, Spilich G. Changes of attention and memory in a group of patients with multiple sclerosis. *Clin Neurol Neurosurg* 2002; 104: 221–27. PMID: 12127658
6. Winkelmann, A., Engel, C., Apel, A., and Zettl, U.K. Cognitive impairment in multiple sclerosis. *J. Neurol.* 2007, 254(Suppl. 2),II35–II42. DOI: 10.1007/s00415-007-2010-9
7. Guimarães, J. and Sá, M.J. Cognitive dysfunction in multiple sclerosis. *Front. Neurol.* 2012, 3, 74. DOI: 10.3389/fneur.2012.00074
8. Brassington JC, Marsh NV. Neuropsychological aspects of multiple sclerosis. *Neuropsychol Rev* 1998; 8: 43–77. PMID: 9658410
9. DeLuca J, Barbieri-Berger S, Johnson SK. The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. *J Clin Exp Neuropsychol* 1994; 16: 183–89. DOI: 10.1080/01688639408402629
10. Schwid, S. R., Goodman, A. D., Weinstein, A., McDermott, M. P., & Johnson, K. P. Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. *Journal of the neurological sciences* 2007, 255(1), 57–63. doi.org/10.1016/j.jns.2007.01.070
11. Filley, C. M. White matter dementia. *Therapeutic advances in neurological disorders* 2012, 5(5), 267–277. doi:10.1177/1756285612454323
12. Mahler and Benson. Cognitive Dysfunction in Multiple Sclerosis, a Subcortical dementia? In: Rao, S. M. (Ed.) (1990). *Neurobehavioral aspects of multiple sclerosis*. Oxford University Press, USA.
13. Benedict RH, Bobholz JH. Multiple sclerosis. *Semin Neurol.* 2007, 27(1):78–85. DOI: 10.1055/s-2006-956758
14. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.
15. World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
16. Jennekens-Schinkel, A., Lanser, J. B. K., Van der Velde, E. A., & Sanders, E. A. C. M. Performances of multiple sclerosis patients in tasks requiring language and visuoconstruction: Assessment of outpatients in quiescent disease stages. *Journal of the neurological sciences*, 1990, 95(1), 89–103. DOI: 10.1016/0022-510X(90)90119-8
17. Amato, M. P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., & Amaducci, L. Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. *Archives of Neurology* 1995, 52(2), 168–172.
18. Kujala, P., Portin, R., & Ruutiainen, J. The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. *Brain: a journal of neurology* 1997, 120(2), 289–297.
19. Amato, M. P., Ponziani, G., Siracusa, G., & Sorbi, S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Archives of neurology* 2001, 58(10), 1602–1606. DOI: 10.1001/archneur.58.10.1602
20. Zivadinov, R., Sepcic, J., Nasuelli, D., De Masi, R., Bragadin, L. M., Tommasi, M. A., & Pozzi-Mucelli, R. S. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2001, 70(6), 773–780. PMID: PMC1737379
21. Piras MR, Magnano I, Canu E D G Paulus, K S, Satta W M, Soddu A, Conti M, Achene A, Solinas G, Aiello I. Longitudinal study of cognitive dysfunction in multiple sclerosis: neuropsychological, neuroradiological, and neurophysiological

cal findings. *Journal of Neurology, Neurosurgery & Psychiatry* 2003, 74(7), 878-885. doi.org/10.1136/jnnp.74.7.878

22. Haase, C. G., Tinnefeld, M., Daum, I., Ganz, R. E., Haupts, M., & Faustmann, P. M. Cognitive, but not mood dysfunction develops in multiple sclerosis during 7 years of follow-up. *European neurology* 2004, 52(2), 92-95. DOI: 10.1159/000079937

23. Camp, S. J., Stevenson, V. L., Thompson, A. J., Ingle, G. T., et al. A longitudinal study of cognition in primary progressive multiple sclerosis. *Brain* 2005, 128(12), 2891-2898. DOI: 10.1093/brain/awh602

24. Jønsson, A., Andresen, J., Storr, L., Tscherning, T., Sørensen, P. S., & Ravnborg, M. Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. *Journal of the neurological sciences* 2006, 245(1), 77-85.

25. Amato, M P, Portaccio E, Goretti B, Zipoli V, Battaglini M, Letizia M. B, Stromillo M L, Guidi L; Siracusa G, Sorbi S, Federico A, De Stefano N. Association of Neocortical Volume Changes With Cognitive Deterioration in Relapsing-Remitting Multiple Sclerosis. *Arch Neurol.* 2007 ;64(8):1157-1161

26. Denney, D. R., Lynch, S. G., & Parmenter, B. A. A 3-year longitudinal study of cognitive impairment in patients with primary progressive multiple sclerosis: speed matters. *Journal of the neurological sciences* 2008, 267(1-2), 129-136.

27. Schwid, S. R., Goodman, A. D., Weinstein, A., McDermott, M. P., & Johnson, K. P. (2007). Cognitive function in relapsing multiple sclerosis: minimal changes in a 10-year clinical trial. *Journal of the neurological sciences*, 255(1), 57-63. doi.org/10.1016/j.jns.2007.01.070

28. Glanz, B. I., Healy, B. C., Hviid, L. E., Chitnis, T., & Weiner, H. L. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. *Journal of Neurology, Neurosurgery & Psychiatry* 2012, 83(1), 38-43. DOI: 10.1136/jnnp.2010.237834

29. Strober Lauren B., Rao Stephen M., Lee Jar-Chi, Fischer Elizabeth, Rudick Richard Elizabeth Fischerc, Richard Rudickc (2014). Cognitive impairment in multiple sclerosis: An 18year follow-up study. *Multiple Sclerosis and Related Disorders* 2014,

3, 473–481 doi.org/10.1016/j.msard.2014.03.004

30. Potagas, C., Giogkaraki, E., Koutsis, G., Mandellos, D., Tsirempolou, E., Sfagos, C., & Vassilopoulos, D. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *Journal of the neurological sciences* 2008, 267(1), 100-106.

31. Bsteh, G., Ehling, R., Lutterotti, A., Hegen, H., Di Pauli, F., Auer, M., ... & Berger, T. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis: insights from a 10-year observational study. *PloS one* 2016, 11(7), e0158978. doi.org/10.1371/journal.pone.0158978

32. Drew, M., Tippett, L. J., Starkey, N. J., & Isler, R. B. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. *Archives of Clinical Neuropsychology* 2008, 23(1), 1-19. DOI: 10.1016/j.acn.2007.09.005

33. Huijbregts, S. C., Kalkers, N. F., de Sonneville, L. M., de Groot, V., & Polman, C. H. Cognitive impairment and decline in different MS subtypes. *Journal of the neurological sciences* 2006, 245(1-2), 187-194. DOI: 10.1016/j.jns.2005.07.018

34. Patti, F., Failla, G., Ciancio, M. R., L'Episcopo, M. R., & Reggio, A. Neuropsychological, neuroradiological and clinical findings in multiple sclerosis. A 3 year follow-up study. *European journal of neurology* 1998, 5(3), 283-286.

35. Feinstein, A., Kartsounis, L. D., Miller, D. H., Youl, B. D., & Ron, M. A. Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. *Journal of Neurology, Neurosurgery & Psychiatry* 1992, 55(10), 869-876. PMID: 1431949

36. Sperling, R. A., Guttmann, C. R., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., & Kikinis, R. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. *Archives of neurology* 2001, 58(1), 115-121. PMID: 11176944