Cognitive impairment (CI) in Multiple Sclerosis (MS) has been recognized for over 130 years since described by Charcot in the late nineteenth century. He used the terms “weakening of memory, slow conceptual thoughts and a blunted affect and intellectual life” in his 1877 lectures. The last 70 years have seen numerous papers published on this topic, partly due to improved neuropsychological testing, which is essential in evaluating CI.

Some degree of CI is common in MS. Using neuropsychological testing it affects upward of 45 percent of community dwelling populations. Self-reported CI has been noted, not surprisingly, to be higher in up to 58 percent of the MS population in recent studies in Australia. Summarizing the current status of cognitive impairment in MS is as follows:

• Cognitive impairment is relatively mild on neuropsychological testing in most people with MS.

• The most common cognitive impairments involve complex attention, speed of processing information, short-term memory loss, complex visual-spatial processing, abstract reasoning, and problem solving.

• Basic attention, routine social skills and general language skills, except mild word finding, are usually normal or mildly involved, even if other areas of cognition are more impaired. As a result of spared routine social and language skills, more cognitive impaired individuals can go undetected during brief or superficial social interactions.

• Mini-mental testing (MMSE), the most frequently used office cognitive testing assessment, was mainly designed as a cognitive screen in the elderly and is being used regularly in the MS population. This test has been found to be very insensitive in detecting CI in MS and has been shown to miss severe neuropsychological proven CI in 20 percent of cases.

• Patients with MS who are complaining of cognitive difficulties or are recognized by family and friends to have CI (memory loss, slow comprehension, and personality change), should undergo thorough neuropsychological evaluation to determine cognitive limitations, functional capacity, and emotional status.

• Duration of MS is generally considered a poor indicator of the presence of cognitive impairment.

• Severity of CI does not usually correlate with severity of MS. CI can be a significant symptom in up to 50 percent of recently diagnosed MS and has been well described in the clinically isolated syndrome or initial presentation of disease.

• Cognitive impairment does not correlate overall with physical impairment in this disease.

• Cognitive impairment has not shown a consistent correlation with white matter burden on MRI. However, this is changing because new MRI techniques can show cortical gray matter lesions not seen on routine MRI. Massimiliano et al. showed that cortical lesions on MRI obtained on double inversion recovery sequences and cortical atrophy strongly correlated with CI. Future studies looking at cerebral cortical MS lesions may well change some of the current cognitive information in this disease.

Multiple Sclerosis and Mild Cognitive Impairment

What are the cognitive impairments in MS and why are the terms dementia and Mild Cognitive Impairment (MCI) rarely used?

By Ronald Devere, MD
Secondary progressive MS is an indicator of greater likelihood of CI. Chelune et al., found that CI is seven times more likely in secondary progressive MS than in relapsing and remitting.

Once CI becomes clinically apparent, it tends not to remit. The only exception is when it occurs solely as a temporary symptom during an exacerbation. This form is usually sudden in onset, coinciding with the onset of neurological physical symptoms and remits when the exacerbation is over.

Most studies have suggested a relative stability of cognitive impairment for up to four years. Pirasm et al., in a small sample of MS patients, showed that cognitive deterioration over an eight year period was limited to impaired long term memory and general intellectual function in fifty eight percent with relapsing, remitting MS. Other areas of cognitive function were very stable. Other studies have suggested a more predictable very slow decline, especially those with a progressive form of MS. Overall, there is difficulty predicting change in a specific individual over time. Amato et al concluded that cognitive deterioration in MS occurs much more slowly and less consistent than in Alzheimer’s disease. This is an important point because cognitively impaired MS patients are likely to be stable enough or so slowly progress, that they have been shown to benefit significantly from cognitive rehabilitation.

Now that I have given some of the more important information on MS cognitive impairment, another important question is: How does CI really affect the quality of life (QOL) in MS patients? Most studies have been contradictory. One recent study by Glanz et al., using a standard cognitive evaluation and a self reported QOL questionnaire in early MS, with depression controlled, found that QOL was weak or negligibly related to cognitive function. A more recent study by Baumstark et al., including all MS subtypes found the same conclusion. These studies stated that the key point in evaluating cognitive impairment and QOL in MS is recognizing that fatigue and depression need to be controlled, because they are independent predictors of QOL, regardless of the cognitive impairment. This point was stressed in past studies as well.

Pharmacological Treatment of Cognitive Impairment in MS

Is there any evidence that specific medication is effective in cognitive impairment in MS? Greene et al., studied Donepezil (Aricept) 10mg over a 12 week study in 17 MS cases. It showed statistically significant improvement in attention, memory, and executive function. Another double blind placebo randomized control study, studied Donepezil (Aricept) for 24 weeks in 69 patients. There was significant improvement in memory, although the patients were only mildly impaired. One double blind random placebo controlled study looked at Rivistigmine (Exelon) for 12 weeks in 60 cases and showed slight but significant improvement in memory in both patients and placebo group. The conclusion at this time is that the findings suggest some possible benefit of Donepezil, less so Rivistigmine, in MS cognitive impairment. More long-term studies of these and other medications (galantamine, memantine) are needed.

There are a couple of points to consider regarding the above studies. Unlike Alzheimer’s disease, there has been no solid pathological evidence that there is a deficiency of Acetylcholine in MS cognitive impairment. It has only been presumed based on the widespread demyelinating and axonal changes in MS plaques. This is not necessarily a reason not to try these medications in MS. Secondly, the patients enrolled in many of the above trials were not characterized as dementia or MCI and very little activities of daily living information were presented. This made it very difficult to decide what type of cognitive impaired patients were evaluated. In addition the trials were very short, lasting 12 to 24 weeks. We know from amnestic MCI studies, which were over a three-year period, that possibly only Aricept might be of one to two year(s) benefit in delaying the development of AD. We also know from many studies that the cholinesterase and glutamate inhibitors have a modest effect on all stages of Alzheimer’s disease.
Since the conclusion of all the MS studies have shown minimal or no benefit of these agents in cognitive impairment, these studies should be repeated with longer durations when proper cognitive classification is done.

**Dementia in MS**

Although the majority of patients with MS have mild cognitive changes, many develop more severe changes, as previously mentioned and warrant the use of the term “dementia.” Estimates of the rate of more severe cognitive impairment varies between five percent and 30 percent.\(^9\)\(^{34}\)\(^{35}\) However, reviewing the titles and contents of many published articles on cognitive impairment in MS, it is surprising that the term “dementia” was rarely used and the concept of Mild Cognitive Impairment (MCI), which has become increasing popular over the last 15 years, is non-existent. A search for dementia in MS specifically yields a few articles. In one\(^{36}\) publication, the author states: “Determining a precise rate of occurrence of dementia in MS via review of the scientific literature is difficult, as the term, ‘dementia’ and ‘cognitive impairment’ are used interchangeably. Also other loosely defined terms such as ‘global’ impairment or ‘severe’ cognitive impairment are frequently used.”

The definition of dementia is currently undergoing changes because the old definition, published in DSM IV 1994, has become outdated in relationship to the increased information acquired about cognitive disorders and introduction of the term MCI in the last ten years. The Alzheimer’s Association in 2010 proposed new updated criteria for Alzheimer Dementia and its relationship to MCI. These criteria have recently been adopted after a year review by several research groups and should be incorporated in the revised DSM criteria for dementia. The old DSM-IV criteria for dementia due to other medical conditions are:

A. Development of multiple cognitive deficits:
   a. Memory impairment
   b. One or more of the following: aphasia, apraxia, agnosia, impaired executive function

B. These deficits cause significant impairment in social or occupational function and represent a significant deterioration from the premorbid state

C. Deficits are due to direct physiological consequences of a general medical condition (such as MS)

D. Impairments do not occur as a result of delirium.

It is important to note that the term progressive decline is not mentioned, since many of us know that most of the degenerative disorders like Alzheimer’s disease, frontal dementia, Parkinson’s and Lewy body dementia are progressive, unlike many MS moderate to severe cognitive impaired cases, which can remain stable for many years despite no specific cognitive treatments. MS cognitive impairment rarely develop major language impairment or impaired basic orientation. One study\(^{4}\) found that MS dementia acted similar to a subcortical dementia like Parkinson’s or Huntington’s disease, which includes personality change, mood disturbances, slow thinking, decreased attention, problem solving and problems with memory retrieval. This was also echoed by others.\(^{37}\) Others have stated that MS dementia is a form of frontal dementia.\(^{38}\) One article published in 2005,\(^{39}\) reported that nursing home residents with MS and dementia are usually admitted at an older age (10 years) than the non-demented MS patients and are less likely to have physical impairments but much more likely to have mood and behavioral problems. They suggested these cases may represent a “cortical variant” of MS characterized by progressive dementia and emotional difficulties with late onset of other neurological impairments leading to physical disability. Based on the excellent review by Longley\(^{40}\) and this literature review, there are some possible reasons for the very infrequent use of the terms “dementia” and “MCI” in cognitive impaired MS patients.

- The term dementia in our society carries a terrible stigma of a progressive untreated cognitive deterioration, with strange and disturbing behavior, ending up in a nursing home to die. This term
has in general been used to apply to the older population and has led to very negative reactions in families and patients, because MS occurs in a much younger population and many who are more cognitively impaired usually articulate well and are capable of light social interaction.

- Patients with MS are usually in the early years of their careers, looking after young children and trying to work or run a household. With the help of their physician, they are also trying to manage a progressive or fluctuating degree of physical impairment. The sense of hope in the face of this unpredictable neurological disorder is very strong, not supported by the perceived term, dementia.

- The management and treatment of MS patients in the past 15 years has become very complicated and requires expert knowledge of the disease and its management. Numerous more potentially toxic medications with significant side effects are becoming more available. I am not sure how many general neurologists are treating these complicated patients, but more and more “experts” in clinical and research MS are available in private and university related practices.

In my experience the majority of MS patients with cognitive disorders, regardless of severity, are regularly followed and treated by MS specialists and many general neurologists. The MS specialists are doing a lot of the clinical research and publishing many of the scientific papers. Their overall experience in using the terms MCI and dementia in their specialty practice may be limited. The cognitive testing in many published articles and in everyday practice of MS patients may or may not be done by neuropsychologists who are experts in the terminology of dementia and MCI.

- The term MCI has been recognized for over 10 years. It has been predominantly used in the neurodegenerative pre-dementia arena, but the term is also being used in non-degenerative disorders like multiple strokes. MCI is defined as a cognitive disorder with little or no impairment of activities of daily living, and stands between normal cognitive function and dementia. Any one or more areas of (impaired memory, executive function, speech/language, personality or visual perception) are acceptable under the category as long as they meet the strict definition of minimal-to-no impairment of activities of daily living. Amnestic MCI has been shown to progress to AD in 75 percent of cases over a five-year period. Non-amnestic MCI has been shown to develop into AD in 55 percent, but other disorders like Parkinson’s, Lewy body, frontal and multi-infarct dementia can develop in others. Some cases remain the same, never progress or rarely improve. In 2004, a study divided amnestic and non-amnestic MCI into single or multiple domain. This was done, so all aspects of cognitive function were included (memory, executive function, speech, language, personality, and visual perception. This classification recognized that individuals with MCI may have more than one category of cognitive impairment, with no effect on ADLs and so they did not meet the criteria for a diagnosis of dementia. This information was important to document because multiple domain cognitive impairment was at times more likely to progress to dementia in a shorter time period.

- The dementia and MCI terminology have been very helpful in interpreting cognitive dysfunction, ADLs and quality of life, not only for research purposes but to counsel and educate patients and family about the disorder, in decisions on appointing a Durable Power of Attorney (DPOA), and making competent financial and estate decisions.

Suggestions and advantages in incorporating cognitive abnormalities in MS into the mainstream of terminology used in other causes of cognitive impairment:

- Update clinical and research MS specialists and general neurologists in the terminology of dementia and MCI as it relates to MS and other causes of cognitive disorders especially Alzheimer’s, Parkinson’s, and frontal dementia and how they differ from MS dementia. This can be done in the various general and MS specialty journals or symposia on MS with assistance from members of the Cognitive and Behavioral section of the AAN. If not already done, reviews by the
legal system should be included in the same venues to discuss DPOA for health and estate decisions and legal guardianship and how it relates to cognitive impairment in the younger MS population.

- Since neuropsychological testing is so important in the diagnosis of cognitive dysfunction in MS, it is very important that the neuropsychologist, who is well trained in this terminology, be reminded that they should use this terminology in their summary and final opinion in their reports and help in education.

- It is also important that physical impairment not be included in impaired ADLs as it relates to cognitive impairment. Including physical impairment could under or over diagnose the cognitive effects on ADLs. For example, impaired memory in the presence of weak and numb arms could mistakenly be represented as inability to do finances and reconcile a check book for cognitive reasons. Memory impairment alone does not usually affect important financial and estate decisions, appointing a DPOA, and only mild cognitive supervision is normally necessary. MS patients, who meet the cognitive and ADL criteria for dementia, will likely require full time care and supervision and be unable to make decisions in their best interest regardless of the status of physical impairment.

- Thorough education is necessary to patients, families, other caregivers and MS societies, so they fully understand the terms dementia and MCI as it relates to MS. Attempts should also be made to erase some of the negative stigma or misunderstanding of the term dementia. Longley stated a useful layman’s definition of dementia for use with individuals with MS: “It is a broad term to describe the loss of memory, thinking, some social skills and usually normal emotional reaction. It would also be very helpful to stress the significant difference in clinical presentation and progression over time, between MS dementia and Alzheimer’s dementia.” The legal system should provide education to MS physicians, caregivers, patients and MS societies as relates to DPOA and legal guardianship.

- Careful, discrete, and appropriate use of the term dementia has been shown to be at times positive. This term stresses the severity of an individual’s cognitive impairment. It can reduce the risk that the person’s cognitive impairment may be dismissed because of their good initial presentation or because of their young age group.

- The proper use of the dementia term, where appropriate, can help the person obtain retirement benefits, a disability insurance claim, or help collect long-term care insurance if previously purchased.

Summary and Conclusion
The clinical knowledge relating to diagnosis and treatment of MS has mushroomed in the last 15 years. Cognitive impairment in MS has been well studied for many years and is briefly summarized in this review. Neurology still has a long way to go in pharmacological treatment to improve or arrest CI in MS. It is time to put cognitive abnormalities recognized in MS into a more common, defined classified terminology, such as dementia and MCI, instead of the general non-specific terms of “cognitive impairment or global cognitive deterioration,” so we can all better understand our patients’ cognitive impairment and capabilities as they relate to ADLs and make efforts to separate this from physical disability.

The regular use of this terminology will require further education of patients, caregivers, MS societies, clinical and research MS specialists and non specialists who continue to treat this disorder. This information should be stressed in neurology residency training. It will require sensitivity and dispelling myths that are associated with these terms, especially dementia.

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