Mellen Center Approaches: Identifying and managing cognitive disorders in MS

Framework: Cognitive dysfunction is common in the MS population. It affects quality of life and correlates with worsened disease outcome. Our approach is to try to systematically identify and treat this problem early and effectively.

How common are cognitive disorders present in MS?
The prevalence of cognitive impairment in MS is estimated to be between 40 and 65 percent (Bobholz and Rao, 2003). The cognitive abilities most often affected include episodic memory (recall of previously studied information, like a shopping list or story), working memory (temporary on-line maintenance and manipulation of information), divided attention (multi-tasking ability), and speed of processing. However, there is considerable variation in the neuropsychological presentation of MS patients. For example, one study identified six distinct cognitive profiles among patients with relapsing MS entering a trial of interferon-β1a (Fischer, 1999). The largest subgroup, which included 34% of the sample, was cognitively intact. Only 2% showed global cognitive impairment across multiple cognitive domains. The remainder showed circumscribed deficits in two to three cognitive domains.

Do physical disability, disease course, and disease duration correlate with cognitive dysfunction in MS?
Level of physical disability, as measured with the Expanded Disability Status Scale (EDSS), has at best a modest correlation with severity of cognition in MS. This is not surprising since the EDSS is heavily influenced by non-cognitive signs and symptoms, such as ambulation. Several studies have shown that cognitive dysfunction is greater in secondary progressive than in relapsing-remitting MS (Gaudino, Chiaravalloti et al., 2001).

Cross-sectional studies have found only a modest relationship between duration of the disease and extent of cognitive impairment. As noted above, this is likely due to the inter-patient variability in the presentation of cognitive disorders. It is important to note that cognitive changes can occur early in the course of the disease (Deloire, Salort et al., 2005) and, in some patients, may never occur. Longitudinal neuropsychological studies of MS patients studied over an extended period of time; in contrast, suggest that approximately 5-10 percent of patients experience a discernible worsening of cognitive functioning over the course of a year (Amato et al., 2001). We note that unlike patients with progressive dementias, MS patients with cognitive impairment can be stable for years and they may benefit from strategies to minimize the effect of cognitive disorders on their day to day function.

For the above reasons we also do not assume that patients with physical disabilities have cognitive impairment, nor do we assume that those without physical impairment are cognitively intact.

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**Do abnormalities detected on brain MRI scans correlate with cognitive dysfunction in MS?**

Compared to demographic and disease variables, neuroimaging indices correlate relatively well with cognition in MS. Several studies have demonstrated an inverse relation between cognitive performance and number or volume of lesions on conventional MRI, including T2-weighted or fluid-attenuated inversion recovery (FLAIR) imaging (Rovaris and Filippi, 2000). Regionally specific relations between lesion volume and cognition have been reported. For example, one study showed specific relations between frontotemporal lobe involvement and executive functions, like conceptual reasoning (Arnett, Rao et al., 1994). Some studies have suggested that brain atrophy is a better predictor of cognitive impairment in MS than lesion volume (Bermel, Bakshi et al., 2002; Benedict, Weinstock-Guttman et al., 2004). Longitudinal studies have shown a relation between progressive brain atrophy and cognitive changes patterns in MS (Hohol, Guttmann et al., 1997). There are occasional patients with subacute cognitive changes that correlate with the presence of new lesions, so that a new complaint of cognitive dysfunction may prompt further imaging to assess for disease activity. In addition there are patients with prominent cognitive symptoms with limited lesion burden or atrophy on brain imaging. In such patients we would assess carefully for other factors such as medication, sleep disturbance and depression which may masquerade as cognitive deficits (See below).

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**Do cognitive disorders correlate with other factors related to MS (for example, depression, fatigue, sleep disorders)?**

Emotional problems, sleep disorders and fatigue are significantly more common in individuals with MS than in the general population. Although the relationship among these symptoms may be complex, depression has been reported to affect cognitive test performance in the areas of rapid information processing, working memory, and executive function in MS patients (Arnett, Higginson et al., 2001). Although subjective reports of fatigue do not necessarily correlate with observable deficits in cognitive function, decrements in cognitive performance occur during sustained mental effort and after completion of cognitively challenging tasks in MS patients (Krupp and Elkins, 2000; Schwid, Tyler et al., 2003). It is reasonable to assume that patients’ performance may be compromised if they are significantly depressed, fatigued, or sleep deprived during cognitive testing.

There are many medicines used in MS care that may have a negative impact on cognition. We assess these medicines in our patients with cognitive deficits and consider whether they can be changed to alternative medicines or whether they can be weaned off. Medicines that have such an impact include steroids (particularly IV high dose solumedrol), anticholinergics such as oxybutynin, tricyclic antidepressants, sedatives, beta blockers, muscle relaxants, etc.

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How can cognitive disorders be detected in the clinical setting?
One method for identifying cognitive dysfunction is to administer rating questionnaires to patients and their family members. One such scale is the MS Neuropsychological Screening Questionnaire (MSNQ), a 15-item self- and informant-report inventory (Benedict, Cox et al., 2004). Results suggest that informant ratings of cognitive problems are more likely to correlate with objective neuropsychological tests than patient self-reports. Unfortunately, informant ratings are not always available in the clinical setting.

An alternative approach is to use a brief cognitive screening examination. One commonly used test, the Mini-Mental State Examination, has been found to be insensitive to the cognitive impairments in MS. A number of brief cognitive screening tools have been designed specifically to identify MS patients at risk for neuropsychological impairment. They typically assess a range of cognitive domains, including attention, memory, and information processing, in under 20-30 minutes (Rao, Leo et al., 1991; Beatty, Paul et al., 1995). In recent years, computerized batteries have been used to assess cognition in MS; their superiority as a screening tool relative to traditional paper-and-pencil measures has yet to be reported.

One evidence based review of screening measures for cognitive impairment in MS (Rogers and Paegyres, 2007) recommended the Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Test (PASAT), or the MS Neuropsychological Questionnaire (MSNQ) as valid and relevant screening tests for cognitive impairment in MS.

At the Mellen Center we screen both with items on a self-reported quality of life scale as well as in our review of symptoms. We have not systematically used screening tools in our entire population though this would be a reasonable approach as well.

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What is the role of neuropsychology in ascertaining and monitoring cognition?
The brief cognitive screening batteries described above could be administered by a non-neuropsychologist to determine if an MS patient is experiencing some form of cognitive dysfunction. Such a result is of limited importance, however, if not tied into a specific clinical management issue. For this to happen, it is common to refer MS patients for a comprehensive neuropsychological assessment performed by a board-certified clinical neuropsychologist. Such an assessment typically entails three to four hours of testing and includes a clinical interview. Comprehensive assessments can provide detailed baseline and follow-up data as well as information that pertains to complex matters such as differential diagnosis (e.g., MS dementia versus Alzheimer’s disease in an elderly patient), guidance for rehabilitation or therapies, or determination of disability status. A consensus conference has identified a core battery of tests to guide neuropsychologists in conducting a comprehensive neuropsychological assessment that is tailored to the MS patient (Benedict, Fischer et al., 2002). Referral to a clinical neuropsychologist, board-certified by the American Board of Clinical Neuropsychology, is recommended. Experience in the assessment of multiple sclerosis is preferred, but not essential.

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What non medication interventions exist for cognitive dysfunction?

Nonpharmacologic treatment for cognitive impairment in MS, variously described as cognitive retraining, cognitive remediation, or cognitive rehabilitation among other labels, includes three main approaches: (1) restorative therapies that aim to improve specific abilities, (2) compensatory approaches that aim to circumvent cognitive problems through the use of cognitive strategies, and (3) adaptive approaches that aim to circumvent cognitive problems through the use of external aids and modifications (Amato and Zipoli, 2003). Recent studies have begun to assess interventions specifically designed to improve targeted aspects of learning and memory in MS (Chiaravalloti, DeLuca et al., 2005). One recent study suggested that aerobic exercise is protective against brain atrophy in patients with MS (Prakash, 2010).

In addition to the direct treatment of cognition, it is useful to detect and treat co-morbidities such as depression and fatigue that can influence cognition and quality of life (Amato and Zipoli, 2003; Bagert, Camplair et al., 2002; Bakshi, 2003). Cognitive-behavioral counseling based in neuropsychological principles has been shown to improve insight and social skills, leading to a reduction in disinhibition and social aggressiveness in cognitively impaired MS patients (Benedict, Shapiro et al., 2000).

What medication approaches are there for cognitive dysfunction?

Treatment of cognitive problems in MS has received relatively little clinical or empirical attention in the past. However, recent years have seen the emergence of studies of pharmacologic interventions that have undergone rigorous scientific scrutiny in well-deigned clinical trials (Doraiswamy and Rao, 2004). Prevention of cognitive impairment in MS is an important target of therapy. Disease-modifying medications have been shown to have a beneficial effect on cognition (e.g., Fischer, Priore et al., 2000). Pharmacologic strategies used to treat cognitive impairment in other disorders may have a beneficial effect in MS. A randomized, placebo-controlled study demonstrated a modest but statistically significant benefit of the cholinesterase inhibitor donepezil on memory test performance in MS (Krupp, Christodoulou et al., 2004). It may also be helpful to minimize, when possible, the use of medications with potential adverse cognitive consequences, such as bladder-control medications with anticholinergic effects (Tsao and Heilman, 2005). A randomized multicenter study of memantine 10 mg bid in MS patients with cognitive symptoms shows more fatigue and neurological adverse events than patients on placebo, and no positive effect on cognition. Higher doses of memantine may have more cognitive side effects in this population as well.

Other medications considered for use in this population have not been tested in a randomized trial way. These include activating antidepressants, stimulants, and modafinil. There are no data at present to support the use of these medicines in this setting.

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What do families need to think of when there are cognitive disorders?

Independent of severity of physical disability, cognitive dysfunction can have a major impact on employment and activities of daily living in MS (Rao, Leo et al., 1991). Severity of cognitive impairment, as measured by neuropsychological testing, is predictive of ability to drive (Schultheis, Garay et al., 2002), employment status (Benedict, 2005; Rao, Leo et al., 1991), success in rehabilitation (Langdon and Thompson, 1999), and social skills (Knight, Devereux et al., 1997). It is critical that patients and family members receive accurate information and psychosocial counseling to assist them in coping with these sometimes intractable consequences of MS.

There are specific recommendations available on the assessment and management of cognitive impairment in MS which may be useful to families and patients with such impairment (Benedict Zacharia, et al., 2006).

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Benedict RHB, Zacharia AB, Bednarik PA et al. Assessment and management of cognitive impairment in multiple sclerosis. US neurological disease 2006; volume II: 7-10

