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.

Q. How common are cognitive disorders present in MS?

A. The prevalence of cognitive impairment in MS is estimated to be between 40 and 65 percent (Bobholz and Rao, 2003; Benedict, Zivadinov, 2011). 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. Language, executive, and visuopatial functions are relatively spared. 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-ß1a (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.

At the Mellen Center we specifically inquire about the presence of cognitive symptoms at each visit. This is done both in our previsit screening questionnaire and as part of our review of symptoms for each visit. If this is an issue for the patient or their families, we inquire more deeply into this issue.

Bobholz, JA and Rao, SM (2003). Cognitive dysfunction in multiple sclerosis: a review of recent developments. Current Opinion in Neurology 16(3): 283-8.

Benedikt R, Zivadinov R (2011) Risk factors for and management of cognitive dysfunction in multiple sclerosis Nature Reviews Neurology 7, 332-342

Fischer JS, Rudick RA, et al.(1999) The MSFC: an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Multiple Sclerosis 5(4):244-250

Q. What other factors need to be considered when a patient states they have cognitive problems? (Differential diagnosis).

A. Early in the process of cognitive evaluation for MS patients, other factors should be considered. Standard assessment of laboratory parameters used for general cognitive disorders

should be undertaken (For example, thyroid indices and vitamin B12 level). The patient should have an assessment for depression to ensure that the problem is not primarily related to an emotional disorder (see below). Questions about sleep disturbance should be asked as sleep disorders are common in MS and may affect cognitive abilities. Medication the patient is taking should be evaluated for negative impact on cognition.

Q. Do physical disability, disease course, and disease duration correlate with cognitive dysfunction in MS?

A. 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 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). Unlike patients with progressive dementias, MS patients with cognitive impairment can be stable for years.

In addition, recent case reports have noted cognitive impairment as a sole manifestation of a relapse of MS, with cognitive declines correlating with new lesion formation on MRI imaging.

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

Gaudino, EA, Chiaravalloti, ND, et al. (2001). A comparison of memory performance in relapsing-remitting, primary progressive and secondary progressive, multiple sclerosis. Neuropsychiatry, Neuropsychology, & Behavioral Neurology 14(1): 32-44.

Deloire, MS, Salort, E, et al. (2005). Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 76(4): 519-26.

Amato, MP, Ponziani, G, et al. (2001). Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Archives of Neurology 58(10): 1602-6.

Pardini M,Uccelli A, Grafman J, et al. (2014) Isolated cognitive relapses in multiple sclerosis. J Neurol Neurosurg Psychiatry Published Online First doi:10.1136/ jnnp-2013-307275

Q. 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 frontal 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 (Pardini, 2014). Recent studies indicate that cortical lesions are not only present in early clinical MS, but may be as common as white matter lesions (Lucchinetti 2011). Such lesions and associated tract degeneration may underly some component of the cognitive dysfunction in MS.

Note that 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 masquerading as cognitive deficits (See below).

Foong J, Rozenwicz L, Quaghebeur G, et al. (1998) Neuropsychological deficits in multiple sclerosis after acute relapse. JNNP 64:529-532

Lucchinetti et al (2011) Inflammatory Cortical Demyelination in Early Multiple Sclerosis N Engl J Med 365:2188-2197

Rovaris, M and Filippi, M (2000). MRI correlates of cognitive dysfunction in multiple sclerosis patients. Journal of Neurovirology 6(Suppl 2): S172-5.

Arnett, PA, Rao, SM, et al. (1994). Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. Neurology 44: 420-425.

Bermel, RA, Bakshi, R, et al. (2002). Bicaudate ratio as a magnetic resonance imaging marker of brain atrophy in multiple sclerosis. Archives of Neurology 59(2): 275-80.

Benedict, RHB, Weinstock-Guttman, B, et al. (2004). Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. Archives of Neurology 61(2): 226-30.

Hohol, MJ, Guttmann, CR, et al. (1997). Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. Archives of Neurology 54(8): 1018-25.

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

A. 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. In addition, chronic use of marijuana and related substances can have a negative effect on cognition.

Sleep disorders may be seen with MS and may affect daytime cognitive performance. We do inquire about sleep at the Mellen Center and consider expert evaluation depending on symptoms presented (for example, snoring, restless leg, periodic leg movements, repeated awakenings, etc.)

Arnett, PA, Higginson, CI, et al. (2001). Depression in multiple sclerosis: relationship to planning ability. Journal of the International Neuropsychological Society 7(6): 665-74.

Bolla KI, Brown K, Eldreth D, et al. Dose-related neurocognitive effects of marijuana use. Neurology 2002;59:1337-1343

Krupp, LB and Elkins, LE (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. Neurology 55(7): 934-9.

Schwid, SR, Tyler, CM, et al. (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study. Multiple Sclerosis 9(5): 503-8.

Q. Do relapses cause cognitive impairment?

A. There are documented events where subacute cognitive impairment is the only clinical manifestation of a relapse documented by a decline in neuropsychological function and imaging findings of new lesion formation. A subacute decline in cognition should prompt both a search for factors such as infection, new medication, or emerging illness, or imaging to assess for new lesion activity.

Benedict RHB Characterizing cognitive function during relapse in multiple sclerosis. Mult Scler DOI: 10.1177/1352458514533229

Pardini M, Uccelli A, Grafman J, et al. Isolated cognitive relapses in multiple sclerosis. JNNP doi:10.1136/jnnp-2013-307275

Q. How can cognitive disorders be detected in the clinical setting?

A. ***We note that patient self-report of cognitive deficits is unreliable. Patients with MS who are depressed will report cognitive impairment, while patients with cognitive deficits may underreport their deficits. An informant (family member, close friend) is critical to assist in giving history to document cognitive impairment.*** 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. Performing extensive cognitive testing can be too time consuming for centers with limited staff, yet performing an annual cognitive screen may be necessary as part of ongoing MS care. Langdon and others (2012) extensively reviewed the literature on neuropsychological measures in MS. They determined that the Symbol Digit Modalities Test (SDMT), with the possible addition of the CaliforniaVerbal LearningTest – Second Edition and the BriefVisuospatial MemoryTest – Revised learning trials is a reasonable screen. Their expert panel judged these studies to be preferred over others when rated on psychometric qualities (reliability, validity, and sensitivity), international application, ease of administration, feasibility in the specified context, and acceptability to patients.

The SDMT consists of single digits paired with abstract symbols. The patient must say the number corresponding with each symbol. The test can be administered and scored within 5 minutes. It is a sensitive test of information processing speed that is preferentially affected in MS patients. It is well validated against multiple MRI measures, and has minimal practice effect. One problem with the standard SDMT is that there are not multiple versions, so as a repeated measures test this would be subject to a training effect.

The California Verbal Learning Test-Second Edition comprises a 16 item word list, with four items belonging to each of 4 categories. This is read aloud 5 times in the same order to the patient at a rate slightly slower than 1 per second. This test can be completed in 5-10 minutes including instructions, testing, and responses. This test has also been validated with brain MRI measures.

The Brief Visuospatial Memory Test-Revised Learning T1-3 requires the patient to inspect a 2x3 stimulus array of abstract geometric figures. There are three learning trials of 10 seconds, then the stimulus is removed and the patient is required to draw the array from memory. This study also correlates with a variety of MRI measures.

Other measures which could be used include the PASAT, MOCA test, and others.

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.

Benedict, RH, Cox, D, et al. (2004). Reliable screening for neuropsychological impairment in multiple sclerosis. Multiple Sclerosis 10(6): 675-8.

Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief international cognitive assessment for Multiple Sclerosis (BICAMS). Mult Scler 2012;18:891

Rao, SM, Leo, GJ, et al. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41(5): 685-91.

Rogers JM, Panegyres PK. Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations. J. Clin. Neurosci. 2007;14:919-927

Q. What is the role of neuropsychology in ascertaining and monitoring cognition?

A. 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 specific clinical management. 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. Neuropsychology testing can be particularly helpful if work or school related performance has been questioned, potentially leading to recommendations for accommodations (for example, breaks between tasks, more time for examinations, quieter work space, part time work, etc.)

Referral to a clinical neuropsychologist, board-certified by the American Board of Clinical Neuropsychology, is recommended.

Benedict, RH, Fischer, JS, et al. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. Clinical Neuropsychologist 16(3): 381-97.

Q. What non medication interventions exist for cognitive dysfunction?

A. Non pharmacologic 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). A recent Cochrane Review found low level evidence for the benefit of neuropsychological rehabilitation in MS patients (Rosti-Otajärvi 2014). Variations in study design and conduct precluded a strong recommendation for such rehabilitative strategies.

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). In addition, a single study indicated reduced brain atrophy in patients actively exercising, which might have an impact on cognition (Lovera, 2010).

Compensatory strategies may be helpful. These include a simplified schedule of activities, reminder lists or other strategies, reducing clutter in the household, among others. Where available, vocational rehabilitation may be useful to counsel the patient on alternatives or adaptions which might assist them in the work place.

In general populations various preventive strategies to spare cognition have been supported by epidemiological or clinical trials data. These may be worth discussing with patients concerned about preventing cognitive decline:

a. Regular exercise.

b. Meditation, Yoga

c. Treating hypertension, diabetes, and other vascular risk factors.

d. Smoking cessation

e. Social engagement

f. Vitamin D

g. Cognitive engagement (reading, the arts, etc.)

Data on brain training is limited at the present time.

Amato, MP and Zipoli, V (2003). Clinical management of cognitive impairment in multiple sclerosis: a review of current evidence. International MS Journal 10(3): 72-83.

Chiaravalloti, ND, DeLuca, J, et al. (2005). Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial. Multiple Sclerosis 11(1): 58-68.

Bagert, B, Camplair, P, et al. (2002). Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management. CNS Drugs. 16(7): 445-55.

Bakshi, R (2003). Fatigue associated with multiple sclerosis: diagnosis, impact and management. Multiple Sclerosis 9(3): 219-27.

Benedict, RH, Shapiro, A, et al. (2000). Neuropsychological counseling improves social behavior in cognitively-impaired multiple sclerosis patients. Multiple Sclerosis 6(6): 391-6.

Prakash RS, Snook EM, Motl RW, Kramer AF. Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. Brain Research 2010;1341:41-51

Rosti-Otajärvi EM, Hämäläinen PI. Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD009131. DOI: 10.1002/14651858.CD009131.pub3.

Q. What medication approaches are there for cognitive dysfunction?

A. 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-designed clinical trials (Doraiswamy and Rao, 2004). Prevention of cognitive impairment in MS is an important target of therapy. Some 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). However, a larger multicenter study of donepezil did not confirm this finding (Krupp et al 2011). 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 is limited data to support the use of these medication in this situation.

Doraiswamy, PM and Rao, SM (2004). Treating cognitive deficits in multiple sclerosis: Are we there yet? Neurology 63: 1552-1553.

Fischer, JS, Priore, RL, et al. (2000). Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Annals of Neurology 48: 885-892.

Krupp, LB, Christodoulou, C, et al. (2004). Donepezil improved memory in multiple sclerosis in a randomized clinical trial. Neurology 63: 1579-1585.

Krupp LB, Christodoulou C, Melville P, et al. (2011) Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis Neurology 76:1500-1507

Lovera JF, Frohman E, Brown TR et al. Memantine for cognitive impairment in multiple sclerosis: a randomized placebo-controlled trial. Multiple sclerosis 2010;16:715-723

Tsao, JW and Heilman, KM (2005). Commentary: Donepezil improved memory in multiple sclerosis in a randomized clinical trial. Neurology 64: 1823-1824.

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

A. 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).

Specific considerations to discuss with families include safety (to avoid falls, wandering, injury); financial oversight; and driving safety.

Rao, SM, Leo, GJ, et al. (1991). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 41(5): 692-6.

Schultheis, MT, Garay, E, et al. (2002). Motor vehicle crashes and violations among drivers with multiple sclerosis. Archives of Physical Medicine & Rehabilitation. 83(8): 1175-8.

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

Benedict, RH (2005). Integrating cognitive function screening and assessment into the routine care of multiple sclerosis patients. CNS Spectrums 10(5): 384-91.

Langdon, DW and Thompson, AJ (1999). Multiple sclerosis: a preliminary study of selected variables affecting rehabilitation outcome. Multiple Sclerosis 5(2): 94-100.

Knight, RG, Devereux, RC, et al. (1997). Psychosocial consequences of caring for a spouse with multiple sclerosis. Journal of Clinical & Experimental Neuropsychology 19(1): 7-19.