Major Neurocognitive Disorder in MS: Case Series and Clinical Guidelines

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Introduction

Cognitive dysfunction affects 40% to 70 % (Chiaravalloti 2008) of individuals with Multiple Sclerosis (MS). It may be prominent and cause substantial functional impairment in some patients, compatible with a DSM-5 diagnosis of Major Neurocognitive Disorder (MND) (*Dementia* in other nosological classifications). MND may be highly prevalent in MS clinic populations (Benedict- Bobholtz 2007) but it is often underrecognized (Westervelt 2015) due to perceived stigma, clinicians' time and training limitations, EDSS inadequacy to capture cognitive deficits, lack of correlation with severity of physical symptoms, lack of efficient office cognitive assessment scales, and other factors.

Method

We present a case series of six patients with MND due to MS and summarize the literature on this topic, including clinical guidelines for assessment and management of cognitive impairment in MS, and risk assessment and prevention.

Case Series

Case 1: 51 y/o disabled female, college educated; worked 22 yr in medical administration. MS onset at age 26: motor and sensory symptoms, fatigue; mild cognitive difficulties gradually worsened and had marked progression after a relapse. Unable to work due to cognitive impairment. Carried a RRMS diagnosis. Dependent for all IADLs. EDSS: 3.5. Most recent disease- modifying treatment (DMT): Tecfidera.
Brain MRI: Mild thinning of the corpus callosum and both scattered foci and some early confluence of T2 prolongation in bilateral periventricular (PV) and juxtacortical (JC) white matter (WM). No enhancement. No clear volume loss.
Neuropsychological exam (NPT): Prominent impairments in processing speed, attention/ executive functions (working memory, problem-solving, planning/ organization, set-shifting/cognitive flexibility), and memory (encoding).
Comorbidities: Anxiety & mood difficulties due to MS; no prior psych history. Migraine, hypertension.
Current CNS-active Medications (CNS Meds): Venlafaxine, modafinil, methylphenidate

Case 2: 57 y/o married male, college educated, employed in large retail firm. MS onset: age 48. Cognitive / functional difficulties gradually developed over last few years. Demoted from a managerial position; unable to perform even simpler roles. On medical leave, undergoing disability evaluation. Carried a RRMS diagnosis. EDSS: 2. DMT: Rituximab.
Brain MRI: Diffuse foci of T2 prolongation in bilateral PV & JC WM; no significant T1 prolongation/ enhancement. Mild generalized volume loss with some predominance in the corpus callosum, L> R inferior and posterior frontal cortices, and L>R parietal cortices.
NPT: Prominent deficits in processing speed and executive function; mild difficulties with word finding and speech organization. Increased susceptibility to distraction and decline in delayed recall.
Comorbidities: Benign prior history. 2015-on: Major depression requiring psych admission and intensive f/u.
CNS Meds: Sertraline,hydroxyzine,adderall,amantadine

Case 3: 66 y/o female, high school education, formerly a secretary. RRMS diagnosed mid- 20s. Last few years developed SPMS with cognitive, functional decline. Dependent for all IADLs. EDSS: 3.5. DMT: Riluzole.
Brain MRI: Mild atrophy of the corpus callosum and T1 black holes. Scattered T2 lesions in PV & SC WM. No new or enhancing lesions. PET: not consistent with AD
NPT: Impairments in multiple areas (insight, orientation, naming, memory: storage loss and confabulation). Deficits in executive and visuospatial functions. Behavioral neurology: Multifactorial/ MS- Dementia.
Comorbidities: Major depression, hypothyroidism, hypercholesterolemia
CNS Meds: Zolpidem, baclofen, diazepam, venlafaxine, gabapentin, modafinil.

Case 4: 63 y/o disabled female with an associate's degree, formerly a physical therapist. Only MS symptom: progressive decline in memory and executive function starting in her 50s. Gradual IADLs impairment. PPMS diagnosed at age 61. No DMTs at consult time.
Brain MRI: Multiple T2/ FLAIR hyperintense lesions, cortical atrophy, black holes, atrophy of the corpus callosum. **CSF**: 2 OCBs
NPT: Global impairments; decline in 1 year. Prominent deficits in processing speed and executive fct. Memory impaired at all levels. Naming below expectation; semantic fluency severely impaired. Reduced insight.
Comorbidities: Major depression, Anxiety, ADHD.
CNS Meds: Fluoxetine, quetiapine, trazodone

Case 5: 53 y/o college educated female; retired bank worker. RRMS diagnosed in her 30s. No relapses in recent years. Slowly progressive cognitive decline since diagnosis, worse in last 2 yr. Dependent for IADLs. EDSS: 8.5. DMT: Teriflunomide, Riluzole.
Brain MRI: Diffuse atrophy; moderate PV & subcortical T2 abnormality. Multiple black holes. No enhancing lesions.
NPT: Severe impairments across domains (orientation, executive function, language, memory) with decline in 6yr. Highly perseverative and stimulus-bound. Expressive language dysfluent; spontaneous speech limited. Comprehension: difficulty with 3-step command.
Comorbidities: Depression.
CNS- Meds: Namenda

Clinical Guidelines

Inter-disciplinary Assessment:
-Neurological: MS course and progression, severity and disability level, adequacy of DMTs, treat MS symptoms that may impact cognition (fatigue, sleep, pain/ spasticity, others)
-NPT
-Psychiatric: Treat depression, anxiety, and other comorbidities that may impact cognition
-Psychosocial: Employment/ disability status, power of attorney, health care proxy, caregivers, coping strategies, other
-Brain Imaging
-Functional Assessment of ADLs and IADLs (Lawton & Brody scale or others)
-Risk assessment: Falls; driving; suicidality; financial; exploitation; abuse by caregiver; cooking/ fire; home-accidents; other
-Comorbid medical illnesses: OSA & other sleep disorders; Diabetes; Hypertension; Dyslipidemia; Thyroid disease; Nutritional deficiencies (B12, folate, vitamin D, iron); other
-Medication regimen including CNS depressants and anticholinergic burden; alcohol and substances

Neuropsychological Evaluation & Cognitive Screening
-SDMT: Sensitive (Parmenter 2007), but not to deficits outside of processing speed
-MMSE & MS Neuropsychological Screening Questionnaire: Not sensitive enough
-MoCA: May be a more sensitive screening tool (Dagenais 2013). Correlations with factors derived from NPT
-NPT: Most helpful in identifying scope and severity of cognitive deficits. Two test batteries with wide acceptance: 45 min Brief Repeatable Battery of Neuropsychological tests (BRB-N) and 90 min Minimal Assessment of Cognitive Function in MS (MACFIMS)
-Brief International Cognitive Assessment for MS (BICAMS): New screening tool; needs further validation (Rocca 2015)

Cognitive Impairment (CI) - Pathophysiology
-Classic view of MS as an inflammatory demyelinating disease resulting in subcortical dementia has been expanded (Pflugshaupt 2016)
-MS-related brain pathology is heterogeneous; it also involves neurodegeneration; it can include damage of gray matter (GM) structures (Pflugshaupt; Chiaravalloti)
-Extensive WM lesions (global lesion volume), atrophy of corpus callosum, and WM lesions in specific locations (eg, hippocampi) may correlate with impairment (Fontaine 2015)
-Damage to WM tracts impairs the rapid transfer of information: "disconnection syndrome"; degeneration of neurons in GM impacts a wide range of cognitive functions (Deluca 2015; Rocca 2015).
-Severe cortical dysfunction 2dary to cortical demyelination has been described (Tobin). Cortical variant of MS may be more common than previously thought (Buchanan)
-Brain and cognitive reserve play a protective role (Rocca 2015)

CI - Brain MRI findings
-Brain T1 and T2 lesion volumes and specific lesion location correlate with CIs (Comi)
-CI is related to atrophy (more of deep GM/thalamus than WM lesions) (Houtchens)
-Cortical lesions & atrophy are associated w CI (Calabrese)
-SPMS (marked by increase in atrophy) is associated with greater CI

CI- Psychiatric Illness
-Depression, anxiety, and apathy may contribute to CI (Goretti, Figved, Demaree,Arnett)
-Untreated psychiatric disorders may worsen NPT performance, especially in processing speed, attention, working memory, executive function.
-In addition to antidepressant/ antianxiety agents, stimulants should be considered- possibly earlier than when treating 1ary psychiatric disorders

Treatment
-Donepezil may be helpful for memory, executive function, and other domains. Clinical trials were small, brief, and included MS patients with CI, not necessarily MND (Patti)
-Rivastigmine showed slight benefits, with similar limitations as above
-Memantine showed negative effects
-Stimulants (Morrow 2013) and modafinil (Lange 2009) may help attention, processing speed and executive functioning
-Cognitive rehabilitation may assist in adaptation, sustaining and improving functioning
-Treat etiological and contributing factors (MS; comorbidities; sleep; fatigue; pain; CNS depressant and anticholinergics; alcohol & substances; nutritional deficiencies; other)

Conclusions

There is a solid and growing body of research regarding CI in MS, but specific literature on MND in MS is limited. Periodic screening, cognitive, and functional evaluation may assist in earlier recognition of deficits. Management includes treatment of MS itself, cognitive rehabilitation, pharmacological agents, reducing the burden of contributing etiologies, and preventing risks. Cognitive and brain reserve, early recognition, assessment and treatment of cognitive dysfunction may improve the quality of life of individuals with MS and reduce the risk of MND.

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