Dementia and Multiple Sclerosis

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Short Communication

Cognitive impairment and its links to functional impairment and disability are well-known, although dementia in MS has gotten less attention. Dementia is a disease that occurs when cognitive abilities are significantly impaired and interfere with daily activities. For clinical situations where cognitive or behavioural symptoms " interfere with the ability to function at work or usual activities, represent a decline from previous levels of functioning and performing, and are not explained by delirium or major psychiatric disorder," established based on history and cognitive assessment in clinical settings, the diagnostic guidelines for AD have established criteria for all-cause dementia. In the case of dementia, this decline ought to get worse over time. The Diagnostic and Statistical Manual, Fifth Edition (DSM-5) uses the term Major Neurocognitive Disorder with the criteria that there is evidence of cognitive decline from a previous level of performance in at least one cognitive domain based on concerns from the individual or others, as well as impairments in cognitive assessments that interfere with independence in daily activities [1]. The DSM-5 includes subgroups of neurocognitive disorders (Alzheimer's disease, frontotemporal, Lewy bodies, vascular, etc.) and more specific criteria for major neurocognitive problems brought on by other medical conditions, using MS as an example. Estimates of MS patients with dementia range from 22 to 28%. The DSM-5 criteria for major neurocognitive disorders and the requirement of performance 1.5 standard deviations below the normative mean in two or more cognitive domains in neuropsychological testing were recently combined to form investigational criteria for neurocognitive disorders brought on by MS [2]. This was carried out in recognition of the difficulty in evaluating MS-related cognitive impairment. In an academic MS multidisciplinary clinic, 13.8% of patients met the study criteria for a neurocognitive disorder induced by MS, as opposed to 20.5% when the established DSM-5 criteria were utilised alone [3]. The stigma attached to the term "dementia" in society and its implied connection to neurodegenerative processes when used jokingly make it challenging to diagnose dementia in younger PwMS, among other issues surrounding the diagnosis of dementia in MS, have been discussed by these authors and others. Additional immediate impacts of a dementia diagnosis include limitations on driving, the need for financial and medical care, diminished capacity for informed consent, etc. When a person is diagnosed with a mental illness in their 20s or 30s, it has a profound effect on their lives for decades to come. These issues limit research on dementia caused by MS, which, in turn, limits understanding of the onset of new dementing illnesses in PwMS. According to a recent study based on administrative claims data, PwMS have a higher risk of being diagnosed with both early-onset and late-onset dementia, but the study also noted that it can be challenging to distinguish between cognitive impairments brought on by MS, AD, or other related dementias. Although it makes sense to consider MS as the cause of dementia and progressive cognitive decline, this hasn't been the focus of too many studies outside of case reports. Numerous case reports have described patients with significant cognitive impairment and dementia as well as clinical, radiographic, and neuropathological findings consistent with MS as the predominant cause in the lack of pathological evidence of other neurodegenerative diseases. Neuropathological results in this research frequently include gross cerebral atrophy, corpus callosal, and subcortical demyelinated lesions, which may have a bias for certain brain regions or may be widespread. The pattern of deficits is frequently referred to as "subcortical dementia," with more impaired processing speed, memory retrieval, executive dysfunction, mood disturbances, and neurogenic personality disorder, in contrast to "cortical dementia," which primarily shows impaired memory retention, language, and visuospatial functions, such as in AD. However, as evidenced by cases of dementia and severe cortical dysfunction without the typical history of sensory and motor symptoms, "cortical multiple sclerosis" is beginning to garner increasing attention. The variety in cognitive deficit patterns may make it challenging to identify the aetiology of the disease if the diagnosis of dementia in MS patients is made solely based on neuropsychological performance. The majority of research on AD has focused on MS-related neurodegenerative diseases. Dal-Bianco et al. reviewed 45 autopsy cases of PwMS and found that amyloid plaque and neurofibrillary tangles occur at an incidence rate equivalent to that of the general ageing population [4], concluding that the chronic inflammatory condition of MS does not influence the development of AD. Another autopsy analysis came to similar conclusions after looking at the inflammatory cell infiltrates in 67 MS postmortem from various disease stages and 28 control people without known neurological disease. They found that in older patients, neuroinflammation decreased to levels comparable to controls, whereas neurodegeneration advanced and exceeded controls only in the presence of age-related diseases from vascular disease and AD. The researchers concluded that in older persons, other diseases including Alzheimer's Disease (AD) and vascular disease become the primary causes of neurodegeneration and that the MS-related disease process may come to an end in PwMS who have had the condition for a long time. Research on cases of MS and AD that were similar to one another was done by Luczynski et al (2019). The technique for detecting AD has evolved, and the most recent study paradigm includes biomarkers for amyloid (A), tau, and neurodegeneration from the AT(N) system. Evaluation of AD biomarkers can help provide diagnostic clarification about the coexistence of MS and AD, as demonstrated in the case series described by Flanagan et al. (2014), even though it may not always be practically practicable. Cerebrospinal fluid, amyloid PET, and fluorodeoxyglucose positron emission tomography (FDG-PET) are some of these AD indicators (CSF levels of amyloid 42, total tau, and phosphorylated tau). Because the same results have been demonstrated in MS, there are some restrictions on the evaluation of AD biomarkers in PwMS. Diminished CSF A, found in MS and linked with worse disease progression, is assumed to be caused by MS-related white matter pathology because white matter demyelination coexists with decreased uptake in amyloid PET. Additional studies incorporating direct comparisons of biomarkers between PwMS and/or AD are needed to fully comprehend their significance. However, in vivo data obtained using PET imaging methods has shown a probable connection between MS and AD disorders. In areas of white matter hyperintensities in older PwMS, reduced A binding was observed in comparison to normal-appearing white matter, according to Zeydan et al's studies on Pittsburgh compound B (PiB) PET imaging [5]. It is noteworthy that decreased PiB intake was linked to poorer visuospatial function in PwMS, which has been proposed as an indication of the integrity of extensive networks. According to a second study by Zeydan et al. that showed lower total cortical A deposition in PwMS compared to age-matched HC subjects, the pathophysiology of MS may impede or delay the age-related deposition of A. Tau-PET imaging was performed using the radiotracer 18F-flortaucipir, also known as AV-1451, which did not differentiate between PwMS and

HCs. These results lend credence to the idea that, in elderly PwMS, tau pathology may develop independently from amyloid deposition, and that amyloid accumulation may be cleared up by MS-specific inflammatory processes, such as microglial activation. However, others have suggested that the reduced A protein binding in MS may be linked to age-related impairments in remyelination or demyelination brought on by white matter damage. As was already indicated, unlike the PET results, older MS brains have not yet provided solid evidence of a potential connection between the pathophysiology of MS and other neurodegenerative illnesses. However, preliminary studies have shown that MS brain homogenates and CSF samples include soluble amyloid oligomers, as well as that secondary progressive MS in humans and chronic experimental autoimmune encephalomyelitis in mice, causes hyperphosphorylated tau and the development of insoluble tau. According to these findings, amyloid and tau proteins may contribute to neurodegeneration and MS, as well as the opposite. Future research including ante-mortem cellular and imaging indications as well as post-mortem neuropathology will assist in resolving these potential distinctions and clarifying any shared pathophysiology between MS and AD in the context of older PwMS. Vascular Dementia (VaD) and Dementia with Lewy Bodies (DLB), which are among the most common types of dementia in older adults, are second only to Alzheimer's disease in prevalence. Although the definitions of Vascular Cognitive Impairment (VCI) and vascular Dementia (VaD) have evolved, the general requirements for both conditions remain the same: the cognitive impairment must be present at the same time as a stroke or be accompanied by strong neuroimaging evidence of cerebrovascular disease. PwMS are more likely to have a stroke, which increases their risk of both cognitive declines brought on by MS and VCI. Small-vessel disease-related subcortical vascular dementia, one of the subtypes of vascular dementia, can cause progressive front-subcortical dysfunction, which is similar to MS-related subcortical dementia in that it causes slower psychomotor speed, impaired executive function, and impaired memory recall but preserved recognition. On structural MRI in the subcortical areas, several lacunar infarcts and microbleeds can help distinguish MS from its basic vascular origin and indicate the underlying aetiology. White matter abnormalities (such as periventricular hyperintensities) caused by the small-vessel disease may be mistaken for MS demyelination if not adequately analysed, leading to a misdiagnosis of MS. Confluent demyelinating lesions from MS can mimic the look of small-vessel ischemic illness. Careful examination of the MRI results, combined with the patient's medical history and demographics, can improve diagnosis accuracy by helping to distinguish between vascular and MS lesions as the main source of cognitive impairment. DLB is characterised by cognitive impairments in the cortical and subcortical areas. Though the Lewy body pathology should logically coexist in older PwMS, just like it does in AD, this area is understudied, and no cases of MS with concomitant DLB have been documented. It may be more challenging to identify DLB in persons with MS because three of the primary clinical symptoms of DLB—parkinsonism, visual hallucinations, and rapid eye movement sleep behaviour disorder—have all been linked to MS. Cognitive volatility is the main clinical feature of DLB that is the most difficult to assess and has not been precisely described in MS. Future research is necessary to better understand the clinical DLB phenotype of MS and to look into any interactions between MS and any lingering Lewy body pathology (alpha-synuclein) that might affect elderly PwMS's cognitive and neurological function. For MS patients with dementia and cognitive decline, therapeutic choices are limited. Treatments for AD and DLB frequently include the N-methyl-D-aspartate receptor antagonist memantine and cholinesterase inhibitors. Sadly, these drugs do not appear to be effective in treating cognitive dysfunction brought on by MS, and some studies even indicate that memantine may exacerbate MS-related symptoms. If these therapeutic modalities would be safe and effective in individuals with MS-related dementia or concomitant dementia syndromes, remains to be seen. In conclusion, assessing dementia in elderly PwMS might be difficult since dementia brought on by MS is not systematically examined and defined and because concurrent neurodegenerative illnesses can arise. Due to selection bias, the described case studies might not be representative of older PwMS as a whole. Larger-scale studies are therefore required to fully analyse recognised biomarkers and neuropathological findings in older PwMS with or without dementia, as well as to show the links between clinical presentation, diagnostic tests, and pathology.

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