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Welcome to a new series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short pieces

in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

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What Should You Tell Patients with MS About Their Risk of Developing Dementia?

Case

A 35-year-old man with a new diagnosis of relapsing remitting multiple sclerosis comes for clinic review. His only residual symptom is a bit of tingling in his left leg. His lawyer wife has written a letter to you before the clinic to say that she has read conflicting information on the internet about the effects of MS on cognition and is now very concerned about the risks of dementia. She has not discussed this with him but wanted to find out what the risks were and to have a discussion of this at his next clinic appointment. What should you tell them? There are at least four questions implicit in this scenario. What is meant by 'dementia' (in the context of MS)? How frequently does it occur? What are the implications for this patient? And finally, what should I tell them?

What is 'MS dementia'?

Cognitive dysfunction in MS has a spectrum of severity ranging from mild task-specific deficits to severe global cognitive decline, with most cases falling toward the milder end of that spectrum.¹ As predicted from the distribution of brain damage, in most cases the profile of cognitive impairment predominantly reflects involvement of subcortical pathways, impacting particularly on attention and concentration, processing speed, encoding of new information, working memory, executive functions and affect. This profile is non-specific and (in itself) of limited diagnostic usefulness: similar deficits occur in most 'subcortical dementias'. Moreover, the spectrum of cognitive dysfunction in MS is likely to be broader than can generally be captured by conventional screening instruments, extending to affect complex behaviours and aspects of social cognition.² Certain deficits (such as aphasia and apraxia) occur seldom; however involvement of most cognitive domains has been described, and the specific cognitive presentation shows wide individual variation and correlates only loosely with physical disability. In addition, cognitive dysfunction is frequently associated with fatigue, itself a functionally important symptom in MS. Though classical disconnection syndromes are rare, the cognitive effects of MS may reflect at least in part disruption of cortico-subcortical networks, including ascending cholinergic and

other neurotransmitter pathways.^{3,4} In general the severity of cognitive impairment in MS correlates broadly with disease burden, duration and overall severity,^{1,5} though there is no simple relation to longer term functional outcome. The effect of age is more difficult to assess.⁶ Neither brain atrophy measures nor total lesion load entirely account for the extent of cognitive dysfunction in MS.⁷ White matter lesion volume has been shown to be the best MRI predictor of overall cognitive function after five years in primary progressive MS,³ however the role of cortical damage is increasingly recognised.^{3,7} As with any cognitive syndrome, neuropsychometry (if available) is valuable for delineating deficits more fully and for assessing change. Since cognitive deterioration can signal progressive disease in the absence of increasing physical disability, there is a need for simple and reliable cognitive metrics that can be incorporated into the routine assessment of patients.

How frequently does it occur?

Estimates of the frequency of cognitive decline in MS vary depending in part on how it is defined and measured, but it is common – somewhere in the order of 40-70% of patients will exhibit cognitive deficits at some stage during the course. Although the overall prevalence of cognitive deficits increases with disease duration,⁵ significant dementia eventually develops only in a variable minority¹ and even

Table 1: Cognitive dysfunction in MS: at a glance**How commonly does it occur?**

Cognitive dysfunction is common (over half of patients over the course of the disease) but frank dementia is unusual.

How does it manifest?

Typically, memory, attention and executive functions are predominantly affected.

What is the cognitive outlook?

Cognitive impairment tends to correlate broadly with disease stage and overall severity, and with progressive disease, however prognosis in the individual patient is difficult. Heavy white matter burden on initial MRI is a predictor of cognitive decline in the intermediate to longer term. Cognition is not usually the major determinant of overall functional status.

Is it all just MS?

The possibility of a second disease process should be kept in mind, and pursued particularly if cognitive dysfunction is dominant or rapidly evolving in relation to other disease indices, where atypical brain imaging findings (e.g. focal atrophy) are present or if there is a strong family history of dementia

Can it be treated?

Management focuses mainly on mood, fatigue, iatrogenic and other factors that can contribute to cognitive dysfunction. The role of cholinesterase inhibitors and other symptomatic therapies and the impact of disease-modification on cognitive function remain under evaluation.

after follow-up intervals of 10 to 30 years a substantial proportion of all patients (as many as a half in some series) do not exhibit cognitive decline^{5,6} Apparent discrepancies between studies are likely to reflect not simply the duration of the follow-up interval but the particular neuropsychological indices chosen. Although cognitive symptoms are observed across disease subtypes, cognitive decline tends to be more significant in primary and secondary progressive MS, probably reflecting the relative extent of white matter damage. A meta-analysis in relapsing-remitting MS indicates that cognitive decline is moderate in this group and tends to be more severe in older patients and in females.⁸ Dementia as a presentation of MS is unusual enough (<5% of cases in a recent large series from the Mayo Clinic⁹) to call the diagnosis into question. Unfortunately, MS itself is sufficiently common that second pathologies causing cognitive decline do need to be considered: clues to this situation include dementia as an early or prominent feature, a 'biphasic' course where significant cognitive decline supervenes on longstanding MS that is apparently otherwise stable, a strong family history of dementia, or the presence of focal brain atrophy on MRI.

What are the implications for my patient?

For individual patients with MS and their families, cognitive decline understandably bulks large among the most feared accompaniments of the disease and indeed, it contributes importantly to social handicap over and above the degree of physical impairment as well as potentially limiting the scope of physical rehabilitation.⁵ The risk of developing significant cognitive decline in the individual case is difficult to estimate with any precision, at least until the passage of time has revealed the overall course of the disease more clearly. The question of treatment inevitably arises. In principle, cognition should benefit from restriction of accumulated disease lesion load in relapsing remitting MS; however, there is relatively little evidence concerning the cognitive impact of disease modification, perhaps because trials have tended to include cognition as a secondary outcome measure. This means that cognitive considerations alone do not, in general, presently drive therapeutic decision making, though there are indications this may change.¹⁰ Various symptom-modifying agents have been tried in small numbers of patients, including several of the same drugs used for fatigue, however results to date have been largely inconclusive.¹⁴ There is modest evidence for a useful benefit from acetylcholinesterase inhibition (Donepezil) on learning and memory and everyday functioning,¹⁴ though side effects may be relatively more frequent in patients with MS than with Alzheimer's. For the present, the use of cholinesterase inhibitors for MS is not covered by NICE guidelines in the UK, and this seems unlikely to change in the foreseeable future. The evidence base for nonpharmacological cognitive rehabilitation programmes in MS is similarly limited. One important practical issue is to address treatable factors that may contribute to cognitive dysfunction where these arise. One such factor is the drugs used to treat other symptoms in MS: examples include centrally acting spasmolytic agents such as baclofen or tizanidine (which often produce sedation), and anticholinergic agents to treat urinary urgency (agents with relatively lower CNS activity are preferable to oxybutynin). Other key factors are fatigue and depression: both are common in MS, and treatment may substantially improve overall quality of life. The relationship between depression and cognitive decline is not straightforward, since mood alterations may be less severe in patients who lack insight due to cognitive deterioration, while conversely, depressed patients are more likely to report subjective cognitive complaints.

What should I tell them?

In the light of the available information, what should I tell this patient (and his wife)? Unsurprisingly, there is no simple answer to the question of 'dementia risk' (see Table 1): this must take into account the specific characteristics of the individual patient's MS and its evolution. The first step is to try to uncover what is behind the question, and the concerns of the

patient (besides those of his wife); what do they each understand by 'dementia'? Patients in this age group are typically embroiled in a difficult matrix of social, occupational and not least family planning issues. All this needs to be probed gently at the consultation. If indeed the patient wants more information, my policy is to be honest while (ideally) attempting to tread a path between insouciance and despondency. I would tell them that cognitive symptoms are common in MS, but generalised intellectual decline ('dementia' in the traditional and popular sense) is uncommon. Typically everyday memory, concentration and aspects of organisational and planning ability (i.e., executive functions) are most vulnerable, whereas a number of specific cognitive capacities are spared. More precise cognitive prognosis in the individual case is difficult; however, this patient appears to have relapsing-remitting disease which, on current evidence, would place him in a relatively favourable prognostic group. While there is no very effective treatment for cognitive symptoms per se, there is a need for vigilance to ensure that potentially treatable factors that may affect cognitive function in MS are detected and treated wherever possible – and amongst these, one of the most important is mood. Given the current level of clinical and research interest, it also seems fair to suggest that new information relevant to the question will soon be forthcoming. ♦

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