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Commentary

Should we rebrand multiple sclerosis a dementia?

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Multiple sclerosis (MS) is the commonest non-traumatic disabling condition to afflict young adults (Baneke et al., 2013). Given sufficient time MS causes physically disability in the majority of people with MS (pwMS), but has a relatively modest impact on life expectancy reducing it by approximately 8 years (Scalfari et al., 2013; Smestad et al., 2009). As a result MS has a high socioeconomic impact (Kobelt and Gisela, 2004). Evidence has emerged to support early treatment of MS to try and prevent irreversible damage from accruing that is linked to poor outcomes and long-term disability (Giovannoni et al., n.d.). Despite this many countries have restricted access to disease modifying therapies (DMTs), and several of the more effective DMTs have licenses that limit their use as second or even third line therapies (Marziniak et al., 2016) (Ghorab et al., n.d.). In response to this I launched a campaign, using social media, to redefine MS as a preventable dementia with the aim of getting the wider community, in particular the regulators, to re-evaluate their position on access to these more effective treatments. Neurologists are well aware that patients with MS may present with cognitive impairment as the dominant feature and most textbooks of neurology include MS in tables listing the causes of dementia. Therefore the concept of MS being a dementing illness is not novel.

How do we define a dementia? The Diagnostic and Statistical Manual of Mental Disorders (DSM) defines dementia as a loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, not present since birth, and not associated with a loss or alteration of consciousness (American Psychiatric Association, 2000). I would argue that a significant proportion of pwMS would fulfil these contemporary diagnostic criteria for having a dementia (Reisberg, 2006); i.e. loss of cognition severe enough to interfere with normal activities of daily living, being present for more than six months, not present at birth, and finally in the vast majority of cases not being associated with a loss or alteration of consciousness. In the DSM activities of daily living are broken down into four domains, physical, mental, social and occupational. MS is well established as a physically disabling condition; in natural history studies the median time to reach the irreversible disability levels of EDSS 4, 6, and 7 is 8, 20, and 30 years, respectively (Confavreux et al., 2006). The mental or cognitive domain is often overlooked with the majority of pwMS developing significant cognitive impairment with time (Langdon et al., 2010). Cognitive impairment is often present early in the course of the disease, deteriorates with time and is strongly associated with brain volume loss and T1 hypointense lesion volume on MRI (Calabrese et al., 2009; Langdon et al., 2010; Penny et al., 2013). In cross-sectional studies cognitive impairment is found in 30–57% of patients presenting with CIS (Anhoque et al., 2013; Moghadam et al., 2014; Panou et al., 2012; Štecková et al., 2014; Zipoli et al., 2009)and in approximately 25% of patients with radiologically isolated syndromes (RIS)(Amato et al., 2012), or asymptomatic MS. In an Argentinian study of subjects who developed CIS after leaving school it was found that their school performance in the last 3 years of school was poorer than age and sex matched controls implying that asymptomatic MS had affected their cognition years before clinical onset (Sinay et al., 2015). Similarly, approximately 25% of subjects identified as having radiologically isolated syndromes (RIS), or asymptomatic MS,

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have significant cognitive impairment on formal testing (Amato et al., 2012).

The social impact of MS is rarely discussed. PwMS are more likely to be socially isolated (Rimaz et al., 2014), split from their partners (Pfleger et al., 2010; Stenager et al., 1994) and commit suicide (Pompili et al., 2012). Compared to patients with other chronic diseases, such as cancer, patients with MS are twice as likely to be abandoned by their partners (Glantz et al., 2009). Anxiety and depression are common in pwMS (Fiest et al., 2016) and personality changes are well described (Iacovides and Andreoulakis, 2011). These psychiatric manifestations of the disease may explain why MS has a greater impact on interpersonal relationships than other disabling diseases that don't primarily involve the brain, for example rheumatoid arthritis and cancer. The final domain is occupation; approximately 50% of pwMS are unemployed 10 years after the onset of the disease at a stage of the disease with mild physical disability, i.e. approximately 3.0–3.5 on the Expanded Disability Status Scale (EDSS) (Kobelt and Gisela, 2004). The early impact of MS on employment at low levels of physical disability is almost certainly due to 'hidden symptoms', in particular cognitive impairment, depression and anxiety (Strober et al., 2012).

Brain volume loss, which is considered to be a biomarker, or integrator, of neuroaxonal loss in many neurodegenerative dementing diseases, occurs early in MS (Amato et al., 2012; Popescu et al., 2013). The rate of brain volume loss is relatively constant at all stages of the disease including CIS, relapse-remitting and both secondary and primary progressive MS (De Stefano et al., 2010). Brain atrophy is also noted in subjects with RIS and probably explains the associated cognitive impairment that occurs in a proportion of subjects very early in the asymptomatic phase of the disease (Amato et al., 2012; De Stefano et al., 2010; Zipoli et al., 2009).

As part of the "rebranding MS a dementia" campaign on our blog (www.ms-res.org) I did two short online surveys to explore whether or not pwMS are aware of MS being a potential dementia and being associated with progressive, and accelerated, brain atrophy. After the an online campaign using social media 67% of respondents agreed that MS is a dementing disease, with only 15% of respondents disagreeing and the remainder being unsure. Eighty percent of respondents had never had brain volume loss, or brain atrophy, discussed with them by their neurologist or other healthcare professionals. Eighty-five percent and 88% of respondents would want to know if they had brain atrophy and progressive brain atrophy, respectively. Importantly, 77% of subjects stated that this knowledge would affect their choice of DMT. Since running this campaign and speaking about it at numerous MS meetings I have been chastised that the message is too negative and potentially stigmatising for pwMS. In a subsequent survey 62% of respondents agreed that 'rebranding MS a dementia' would be stigmatizing, with 18% disagreeing with this and the remainder being undecided. However, in the same survey 98% of respondents said we should not ignore early cognitive impairment as an important issue in MS. 76% felt the early MS-related cognitive impairment justified the use of an early highly-effective treatment paradigm.

In summary, MS is associated with early cognitive impairment and progressive brain volume loss that markedly reduces quality of life, daily functioning (Glanz et al., 2010) and employability (Rao et al., 1991) of pwMS. Despite the message that MS is a dementing illness being a negative one, unless pwMS and their families are made aware of this issue how can they weigh up the risks and benefits of DMTs; in particular the more effective DMTs, which generally come with more risks, but have been shown to greatest impact in reducing the rate of brain atrophy? I have tempered my message and now refer to MS as a **'preventable cause of dementia'**. I am not prepared to hide these facts from my patients. If pwMS are expected to make informed decisions about therapies with potentially life threatening adverse effects they need to know about the consequences of untreated, or undertreated, MS. In my opinion the days of the paternalistic healthcare professional are long gone; what we need are open and honest partnerships with our patients (Giovannoni et al., 2011). This does not mean that one size fits all and where necessary a paternalistic approach to the management of specific patients with MS may be needed (Rosenbaum and Lisa, 2015); in my personal experience this is the minority of patients and requires a judgement call, which is why the practice of medicine remains an art rather than a science.

Conflicts of interest

GG has received compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

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