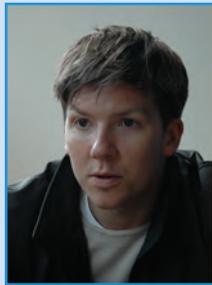


Debate: Does Progressive Multiple Sclerosis start on Day 1?

Report from a satellite symposium at the 2013 Annual Meeting of the Association of British Neurologists (ABN), Glasgow, 24th May 2013.



Chair:
Professor David Bates
Newcastle University,
Newcastle.



Debater: Dr James
Overell, Institute
of Neurological
Sciences, Glasgow.



Debater: Dr Belinda
Weller, Western
General Hospital,
Edinburgh.

The views expressed are those of the speakers in the context of a debate and are not necessarily those of the meeting sponsors.

Introduction

Multiple sclerosis (MS) is a chronic, clinically heterogeneous condition with an extended trajectory that can affect individual patients in many different ways depending on the location(s) of the lesions and the rate of progression. Clinically, most MS patients will present with a relapsing-remitting disease course that can last for decades followed by a 'subsequent' secondary-progressive phase, where relapses become less prominent and relentless neurological decline ensues.¹ In accordance with this model, the current treatment of MS has been mostly focused on the management of relapses and most MS drugs are aimed at reducing new inflammatory demyelinating lesions.

However, whereas MS was once considered to be the "prototype immune-mediated demyelinating disease",² we now also know that axonal degeneration is a major cause of irreversible neurological disability in MS patients.² The exact relationships between inflammation and neurodegeneration, and their relative contribution to disability remain controversial. A key question is whether there is an inevitable and continuing injury to the CNS that starts early on in the disease course?

Yes – Pathological progression starts at Day 1

Dr James Overell began the debate by reviewing the evidence that diffuse pathological changes are apparent in patients with very early MS. He challenged the dogma that inflammation is the cause of axonal and neuronal degeneration in multiple sclerosis, and instead argued that there is a close association between inflammation and neurodegeneration in all types of lesions (active, inactive) and at all MS disease stages. The evidence shows that both axonal damage and inflammation are present early on and that both progress over time.³ Dr Overell also reviewed the accumulating evidence that brain atrophy occurs early – it is present even in patients with clinically isolated syndrome (CIS) – and that atrophy correlates with progression of disability.⁴ Conversely, a recent review of natural history studies highlighted the apparent dissociation between relapses and disease progression.¹ In these studies, the progressive course was found to be independent of relapses either preceding the onset of relapse-free progression or subsequent to it.^{1, 5} Moreover, the site of the original attack is not usually where progression begins.⁵ Dr Overell argued that such findings are important as they suggest that in addition to targeting relapses, it is also crucial to target the progression of the disease. Importantly, recent studies in patients with relapsing-remitting MS show that new treatments may impact atrophy and progression, but with less impact on relapses.^{6, 7}

No – Clinical progression does not start at Day 1

Countering the debate, Dr Belinda Weller argued that when progression is defined clinically as "the onset of insidiously worsening and irreversible neurological function," it cannot be said to start at Day 1. A recent study of a population-based MS cohort showed that patients with RRMS do not inevitably develop a progressive disease course, indeed 38% of patients with RRMS did not develop progression by age 75.⁸ Dr Weller argued that, in her experience, significant numbers of patients have an attack and have abnormalities on MRI – but do not come back to the clinic as they continue to do well over many years. She argued that the patients who attend clinics and are enrolled in clinical trials represent more severely affected patients, and that there is a 'hidden' population of people with MS who do not need to come in for treatment.

Dr Weller discussed that while cognitive dysfunction is often used to support the idea that progression starts from day 1, cognitive dysfunction is common in MS, is related to the location of lesions and may already be seen in CIS, and in early-stage RRMS.⁹ Dr Weller noted that it is very difficult to disentangle the effects of aging from those of MS progression – but it does appear that pre-existing cognitive impairment represents the major risk for further cognitive deterioration.

Reaching consensus

The discussion following the two presentations noted that the debate came down to how progression was defined. When defined clinically, many patients can do well for decades and do not develop progressive MS. However, when defined radiologically or pathologically, it is clear that axonal damage and atrophy occurs early on. While the clinical course of MS differs widely between patients, it is likely that there will be some underlying disease progression – albeit at very different rates.

Both speakers agreed that both relapses and progression deserve consideration and treatment as appropriate to the individual patient. When MS is diagnosed early enough, effective treatment can lead to the reversal of disability.

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