

## Debate & Analysis

# Delayed diagnosis of multiple sclerosis in males:

may account for and dispel common understandings of different MS 'types'

### INTRODUCTION

Multiple sclerosis (MS) is a long-term neurodegenerative condition that affects functioning of the central nervous system, and estimates of its prevalence range from 1–2.5 million people diagnosed worldwide.<sup>1,2</sup> Just as the central nervous system mediates a breadth of bodily functions, MS can manifest in varied ways, often leading to confusion as to whether ill-health is caused by MS or something else.

MS trajectories vary between individuals, and different MS 'types' are commonly used to describe patterns. Relapsing remitting MS (RRMS) refers to short-term exacerbations (relapses) and recovery (remission); secondary progressive MS (SPMS) develops after RRMS and describes long-term permanent neurodegeneration. Primary progressive MS (PPMS) also refers to long-term permanent neurodegeneration, but *without* a relapsing remitting stage preceding it.<sup>3</sup>

### LIMITED CONCEPTUALISATIONS AND EXPLANATIONS

Although these different MS 'types' are commonly referred to within professional and lay circles, individuals' trajectories do not always fit comfortably into their descriptions,<sup>4</sup> no biomarkers have been identified to distinguish between them,<sup>5</sup> and they are not recognised as subtypes in the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10).<sup>6</sup>

Internationally MS appears to be more prevalent in females than males<sup>1,7</sup> and the difference in ratio seems to be rising,<sup>8</sup> except in the case of PPMS, where those diagnosed are more likely to be male and older.<sup>9</sup> Previous research indicates no clear cause for apparent sex differences, but the speed in which ratios are increasing has led some to argue that it is due to environmental factors (for example, changes in females' lifestyles) rather than biological ones,<sup>8</sup> although evidence to conclusively support this hypothesis is lacking.

### EXPANDING OUR THINKING TO CONSIDER SOCIAL FACTORS

This article questions whether we ought to stop looking to biological and environmental factors to explain sex differences and consider if apparent patterning is instead

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due to variance in *when* females and males are diagnosed; that is, a social construction and nothing to do with the pathology of the disease itself or gendered interactions with environmental influences either.

### COULD MS BE A GENDERED CONDITION?

Previously it has been argued that some conditions — such as autism, heart disease, and breast cancer — are gendered; that is, they are associated more with one sex, which potentially leads to missed or later diagnosis for those whose gender is not typically associated with that condition. So, for example, boys may be more likely to be diagnosed with autism because it is recognised sooner in males, resulting in missed or later diagnosis in females. Such gendered associations may not only originate from various influences (such as biological, environmental, or social influences), but also lead to delayed or missed diagnosis in one sex due to gendered associations. There is also the issue of when males and females present. It is widely understood that males' help-seeking behaviour is often delayed for various reasons,<sup>10</sup> thus potentially hindering diagnostic processes.

If MS is a condition that is associated with females more readily — or in which males present later — then it may be that males are diagnosed later. If we disregard the different 'types' of MS, and broadly consider MS trajectories as initially having a relapsing and remitting phase, followed by long-term permanent neurodegeneration, and we then consider the possibility that

males are more likely to be diagnosed later than females, then it is possible that males are more likely to be diagnosed during the long-term permanent neurodegeneration phase of the MS trajectory. This would explain why individuals diagnosed with more progressive forms (or PPMS) tend to be male and older. Additionally, this would explain why MS — especially RRMS and SPMS — *appears* to be more common in females and in turn provide support to dispel the presence of different types of MS.

### IMPLICATIONS OF THIS HYPOTHESIS

MS is a condition that is difficult to diagnose due to lack of clear biomarkers, and symptoms that are often vague, intermittent, and varied. A review of MS healthcare services in the UK reported that some diagnoses took over 17 years to be confirmed.<sup>11</sup> Delayed diagnosis is problematic as experiencing medically unexplained symptoms can be distressing,<sup>12</sup> it has implications for accessing support, and — in the case of MS — there are more treatments options available in the earlier relapsing remitting stage, before long-term progression. Examination of this topic has the potential to enable earlier diagnosis of MS in males, allow clinicians to disregard evidence that MS is more prevalent in females during diagnosis investigations, change research priorities (away from sex differences and MS 'types', towards earlier detection of males with MS in primary care and neurology settings), and provide evidence to perceive MS as one condition, albeit a heterogeneous one.

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## FURTHER INVESTIGATION

This hypothesis — although compelling — is one that is not currently based on evidence. However, previous research demonstrates the challenges of defining MS patterns and no clear sex-related biological or environmental influences that shape MS trajectories, therefore this alternative theory warrants further investigation.

A good place to start would be to research the possibility that early MS symptoms in males are more likely to be missed or overlooked in primary care settings (as this is often the first point of contact when experiencing ill-health). Retrospective analysis of the medical records of those with MS may allow identification of symptoms that were not recognised as potential first signs of MS and perhaps diagnosed as something else. However, this approach would rely on the quality of record-keeping and can only apply to those patients who sought help for their initial symptoms. The decision to seek help may be confounded by other factors including individuals' sociodemographic backgrounds (for example, gender).

Delayed help-seeking behaviour in males may be a key social factor influencing when MS is diagnosed. Considering this, another approach might be to carry out a large-scale survey of people with MS to examine their ill-health prior to seeking help and receiving a diagnosis, and whether potential initial signs of MS were left unaddressed more frequently in males than females. But this method relies on memories spanning decades (even for those newly diagnosed) and retrospective perceptions that ill-health is worth reporting.

We might present a series of vignettes to GPs, of 'healthy' individuals talking about their symptoms, some of which *may* warrant referral to neurology. In recording GPs' judgements about subsequent actions (or lack of actions) we may identify patterns according to the gender of the patients in the vignettes. However, this would assume that males and females communicate symptoms in similar ways, be based on hypothetical scenarios, and may not reflect the reality of consultations.

As this is an area where research is only possible retrospectively (or hypothetically) there are certain methodological disadvantages. We are essentially aiming to identify phenomena that were initially unrecognised (in this case overlooked MS symptoms), which presents a challenge for research. The methods suggested above have flaws but using a combination of these could provide some support to the hypothesis that diagnosis is delayed in males.

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