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Journal of Neurology & Translational Neuroscience

Mini Review

The Mystery of Multiple Sclerosis–is the Answer Right under our Nose?

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Special Issue on
Multiple Sclerosis

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Submitted: 20 February 2014

Accepted: 26 March 2014

Published: 02 April 2014

ISSN: 2333-7087

MINI REVIEW

Multiple Sclerosis (MS) remains the commonest demyelinating disease and cause of paralysis in young adults in the developed world. MS was identified as a distinct neurological disease by the French physician Jean-Martin Charcot more than 150 years ago. Over 100 years ago Marburg described what we now recognize as a partially remyelinating MS 'plaque', and in 2 years' time it will be the centenary of the publication of James Dawson's histopathological monograph 'The Histology of Disseminated Sclerosis', one of the most meticulous and detailed histopathological descriptions of MS [1]. Dawson proposed that the nature of the inflammatory and degenerative changes in MS pointed to the dissemination of a 'toxin' through the perivascular 'lymphatic channels' of the CNS and that the origin of the toxin was probably a focus of infection *outside* the CNS. Dawson also noted structurally *intact* blood-brain barrier within many lesions. Since these early foundations and despite increasingly intensive study, the cause and cure of MS remain elusive.

MS is typically referred to as an 'autoimmune' disease, which is compatible with certain inflammatory histopathological findings. Consequently, much research has been dominated by an animal model of MS, experimental (autoimmune) allergic encephalomyelitis (EAE), which was originally described during Pasteur's early efforts to develop a Rabies vaccine involving the injection of infected nervous tissue and long remained a possible complication of such vaccinations in human recipients. However, immense efforts to identify a common specific autoimmune target antigen in MS, with particular focus on components of the myelin sheath have failed [2]. Currently approved MS therapies based on the autoimmune hypothesis and developed after the amelioration of EAE, such as Natalizumab, Gilenya and Aubagio, with the aim of inhibiting supposed autoreactive immune cells from entering the CNS from the blood or eliminate such cells from the body. These drugs undoubtedly reduce inflammatory activity in the CNS however they show little, if any, efficacy on the progressive phase of MS, which leads to permanent disability. A new, as yet unapproved, treatment, Campath 1-H (Alemtuzamab; Lemtrada), indiscriminately removes all circulating T cells and significantly reduces the number of relapses. Indeed, the fact that some patients treated with Campath1-H have been free of relapses for a decade is not to be underestimated, despite the potentially life-threatening immune complications induced on occasions by the drug. However, Campath1-H has also failed to have any impact on the progression of disability [3]. Therefore, more precisely targeted, safer treatments are required and progress in this direction will likely depend on identifying the cause of MS.

The cause of MS remains elusive. In fact, so elusive, that numerous researchers have argued that MS cannot be a single disease, as defined by Charcot, but a heterogeneous complex of demyelinating diseases, in which "demyelinated plaques may reflect a common pathological end point of a variety of different immunological mechanisms of myelin destruction"[4].

The two major avenues pursued in the search for the cause(s) of MS have been the inheritance of susceptibility and environmental trigger factors. The genetic component of the pathogenesis of MS has recently been extensively investigated. Twin studies are still inconclusive [5] and whole genome association studies have not identified a single mutation associated with MS, in marked contrast with the successful identification of mutations in Parkinson's disease [6]. A large number of environmental factors, such as smoking, lack of vitamin D and EBV [7] are being explored as putative triggers for MS, but links between these factors and MS remain uncertain [8].

Does MS research need to turn a full circle and return to studying the disease as Dawson studied it, by examining the initial lesions in human tissues? Material for such studies has been extremely hard to obtain due to the protracted course of MS, but a breakthrough was made in 1997 when Gay and colleagues collected and examined a panel of autopsy tissues from exceptionally early cases [9]. Some of these were obtained as early as 1 and 2 weeks after the onset of an exacerbation of MS. The findings of this study were unexpected and extraordinary - almost heretical at that time. T cells and infiltrating macrophages, considered to be the main and initiating protagonists in disease pathogenesis (by analogy with EAE), were virtually absent from the identified initiating lesions. Instead, these lesions were characterized by foci of activated microglial cells associated

with complexes of co-locating immunoglobulin and complement. These, in marked contrast to older, actively demyelinating lesions, showed no evidence of blood brain barrier leakage. In 2004, these findings were supported by a similar study of even earlier MS lesions (a case of 17 hours duration) by Barnett and Prineas who described microglial activation and oligodendroglial apoptosis in the absence of T cells [10]. These fascinating histological insights into the early events in MS strongly suggest that the trigger for MS resides within the CNS, or at least enters the CNS through a 'back door' before the infiltrating immune cells enter though the 'main entrance', the latter merely representing the infantry recruited to the battle field well after war has been declared.

The idea of an important agent acting from 'inside' to trigger the pathological processes in MS is not new. In the mid-1990s, a series of studies investigated the presence of endogenous retroviruses in MS tissue [11-13]. Interestingly, as much as 8% of the human genome is made up of retroviral sequences, incorporated into DNA during ancient infections of primate ancestors. These human endogenous retroviruses (HERVs) may remain active and indeed a protein called syncytin, encoded by HERV-W, has been found in demyelinated lesions of MS patients [14]. However subsequent studies, including comprehensive analysis using high-throughput sequencing [15], failed to ascertain whether HERVs trigger the inflammation in MS or simply become activated by inflammatory events in plaques, prompting comments such as that HERVs "are unlikely to cause MS" [16].

So, if the endogenous agents, at least those studied so far, are unlikely to cause MS, there is still a possibility that the culprit sneaks into the CNS through the 'back door'. Interestingly, one of the oldest observations about MS has been its clinical and epidemiological similarity to paranasal sinusitis, both diseases being chronic with superimposed exacerbations [17-19], with greater incidence in colder climates [20-23], and both affecting young females about twice as frequently as young males [24]. It is well known that upper respiratory tract infections, often involving posterior paranasal sinuses, are highly associated with exacerbations of MS [22,23]. Curiously, the ethmoidal and sphenoidal sinuses lie adjacent to the optic nerve, separated only by a thin bony wall [25]. Moreover, this bony barrier is often found to contain numerous perforations and imperfections [25], in which case the mucosal tissue of the paranasal sinus sits directly on the meninges. It is not difficult to imagine how this could be the passage via which pathogens access the CNS. After all, the pharmaceutical industry is racing ahead in developing numerous agents for intranasal delivery into the CNS [26-28]. Remarkably, a recent study seems to have identified a criminal at the scene of the crime in the above mentioned early, pre-demyelinated MS lesions [29]. Using a combination of isoelectric focusing, western blotting and mass spectrometry, Gay has provided convincing evidence of the intrathecal processing of a toxin produced by *Staphylococcus aureus*, sphingomyelinase, in MS patients. Using cryostat sections of early MS tissue the staphylococcal toxin was also identified being processed as an immune complex in the initial primary lesions [29]. If these preliminary findings are confirmed, it is likely that other bacterial toxins and antigens will be found in the CNS in MS cases.

Thus, could the answer to the mystery of MS be right under our nose, or more precisely, behind our noses? If we aim to cure rather than modify MS it is of vital importance to understand the pathological mechanisms operating in the CNS in MS. In a field that has stagnated for many decades, these intriguing findings must not be ignored by the scientific community.

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Cite this article

Sajic M (2014) The Mystery of Multiple Sclerosis–is the Answer Right under our Nose? J Neurol Transl Neurosci 2(2): 1050.