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Invited Review

Helminth therapy and multiple sclerosis

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ABSTRACT

Multiple sclerosis is a common and frequently disabling neurological disease of young adults. It is characterised by recurrent areas of focal inflammation (plaques) in the CNS which give rise to episodic neurological signs and symptoms. According to the hygiene (microbial deprivation) hypothesis, evolutionarily abnormal high levels of sanitation in the environment of the developed world may contribute to disordered immunoregulation in this and other putative autoimmune disorders. Helminths have been shown to augment immunoregulation. On this basis, the possibility of treating multiple sclerosis with live helminths or helminth products has been explored in animal models, natural human infections and phase 1 clinical trials. To date helminth therapy appears safe and preliminary clinical, magnetic resonance imaging and immunological outcomes have generally been favourable. Nevertheless, serious adverse effects are always possible, particularly with live parasitic administration. Follow up studies with safety monitoring, regulatory oversight and objective outcome measures will be required to definitively assess safety and efficacy for this novel class of immunological therapies in multiple sclerosis.

1. Multiple sclerosis (MS)

1.1. What is MS?

Multiple sclerosis (MS) is the most common non-traumatic cause of neurological disability in young adults in developed countries (Noseworthy et al., 2000; Goldenberg, 2012; Nylander and Hafler, 2012). World-wide, more than two million individuals are affected, with a mean onset of approximately 25 years of age (Selmi et al., 2012). MS affects the CNS in a pattern characterised by dissemination in time and space. The disease usually begins with attacks of neurological dysfunction, such as loss of vision in one eye (involvement of an optic nerve), weakness (corticospinal tracts of brain or spinal cord), numbness (sensory tracts), double vision (brainstem), or incoordination (cerebellum). These episodes typically progress for several days or weeks and are usually followed by partial or complete recovery, a pattern that is characteristic of the relapsing-remitting subtype of MS (RRMS). After a decade or more of relapses and remissions, in some patients the pace of disease may change to one of steady progression of disability, constituting the secondary progressive subtype of MS (SPMS). A minority of MS patients will present with a form of the disease characterised by relentless progression from onset, that is, primary progressive MS (PPMS). MS may be mild initially and partially effective medications are available for treatment. Nevertheless, with time many patients will experience substantial and tragic neurological disability related to their disease or serious complications due to immunosuppressive therapy. Better MS treatments are needed.

1.2. MS: Pathology, genetics, epidemiology

Classically, MS is considered a disease of CNS white matter in which there is an autoimmune attack, usually considered to be initiated by dysregulated T cells, on myelin and the myelin-producing cell, the oligodendrocyte. Recently, however, there has been an increased appreciation of wider aspects of MS pathology, including involvement of grey matter, loss of axons, participation of B cells and activated microglia, subtle histological changes in the grossly normal appearing white matter and subtypes of immunopathology (Kipp et al., 2012; Popescu and Lucchinetti, 2012). The major histological abnormality or lesion of MS is the plaque (Fig. 1), a focal area of CNS inflammation and tissue damage (Frohman et al., 2006). In RRMS, new plaques occur at an average rate of approximately 5–10 per year, although there is considerable variation between individuals. Only in about one in 10 plaques is there a "hit" on a critical area of the CNS which gives rise to obvious symptoms and deficits. MS occurs in all ethnic groups; however, surveys have shown that MS is most common in persons of northern European descent. At a finer level, twin studies have shown that, given one twin with MS, the rate of concordance for MS is approximately

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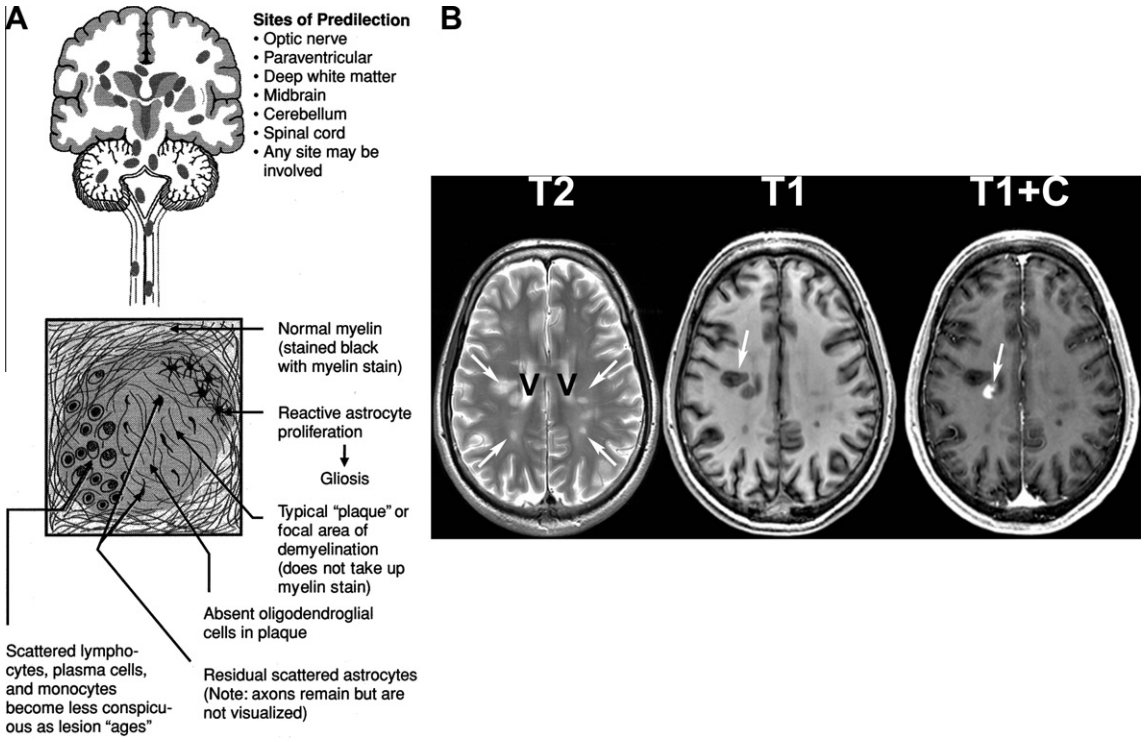

Fig. 1. Multiple sclerosis pathology and magnetic resonance imaging. (A) Schematic representation of multiple sclerosis pathology (reproduced with permission from Fleming, J.O., 2002, Diagnosis and Management of Multiple Sclerosis, Professional Communication, Inc., New York and Oklahoma; modified from original source Chandrasoma and Taylor, 1998). A coronal (face on) view of the CNS is shown (cerebrum at top, brainstem and cerebellum in middle, spinal cord at bottom), with the plaques or scars of multiple sclerosis lesions in white matter indicated by dark oval circles. The inset presents the microscopic pathology of an active multiple sclerosis plaque diagrammatically; the oval plaque consists of an infiltrate of activated immune cells whose attack is primarily directed against the myelin covering of nerve fibres and the cell which produces myelin, the oligodendrocyte. (B) Brain magnetic resonance imaging images for multiple sclerosis (courtesy of Dr. Aaron Field, University of Wisconsin, United States of America). Images are presented in a horizontal orientation (level cross section; forehead at the top of the figure, cerebrum in centre, and back of head to bottom; the cerebral ventricles at the centre of the brain are indicated by the letter "V" and the pathological lesions of multiple sclerosis in the white matter surrounding the ventricles are marked by arrows). Three different settings or pulsing sequences of the magnetic resonance imaging scanner are shown. The image produced depends on the specific pulsing sequence employed by magnetic resonance imaging machine operator and on physical properties of tissue such as T1 or T2 relaxation times and uptake of administered i.v. gadolinium contrast; thus, different magnetic resonance imaging techniques will emphasise or highlight particular pathological changes in tissue. The T2 weighted image shows all multiple sclerosis lesions or plaques, whether active or inactive, and thus is a cumulative account of all multiple sclerosis activity, past and present. The T1 image without gadolinium contrast shows irreversible tissue loss as dark areas ("black holes"). The T1 weighted sequence combined with intravenous gadolinium contrast only demonstrates active lesions with on-going inflammation as bright areas where there is contrast uptake due to breakdown of the blood–brain barrier. Thus, depending on the magnetic resonance imaging sequences chosen, total pathology of all ages (T2 weighted images), irreversible destructive lesions (T1 weighted black holes), or current active pathology (T1 weighted images after i.v. contrast) may be revealed. Most exploratory clinical trials use the rate at which new, active lesions occur during serial magnetic resonance imaging scanning over several months as the primary outcome measure of multiple sclerosis activity.

2% in dizygotes and 30% in monozygotes, indicating the strong, but not complete, role of genetic determination. Genome-wide association studies have identified more than 50 genes with significant associations with MS (Gourraud et al., 2012), and transcriptional analyses have also identified patterns of gene activation associated with MS (Gandhi et al., 2010). These genetic findings in MS have partial overlap with the patterns seen in other autoimmune diseases.

Although the aetiology of MS is unknown, several clues have emerged from epidemiological surveys (Koch-Henriksen and Sorensen, 2010, 2011). In this regard, the prevalence of MS is 5–10 per 100,000 population near the equator, but approximately 200 per 100,000 population above 59 degrees north latitude (Taylor, 2011); a similar gradient (increased MS with increased latitude) is noted in the southern hemisphere. MS also is more common in the developed world than the developing world. Most striking are migration studies which indicate that the place of residence in adolescence or early adulthood strongly influences a person's subsequent risk of MS (Ascherio and Munger, 2007; Orton et al., 2010; McLeod et al., 2012). For example, children migrating from the West Indies to France before adolescence subsequently have an increased risk of MS relative to children with continued residence in the West Indies; this pattern implies that there is either a protective factor in the West Indies or a harmful factor in France (Cabre et al., 2005; Cabre, 2007). Specific determinants which have been posited to predispose people to MS have included lack of sunlight, low vitamin D, Epstein-Barr virus and other viruses, affluence, smoking, high levels of sanitation (hygiene hypothesis, see Section 2) and other factors. Significantly, world-wide there is a strong inverse correlation between helminth infections and MS (Fleming and Cook, 2006) (Fig. 2). The geoepidemiological distributions of helminths and MS may imply that helminths are a protective factor for developing MS or that the absence of helminths increases the risk of MS; alternatively, the inverse association between MS and helminths could merely be an indicator of a more fundamental factor directly implicated in MS causation.

The relative contributions of genes and environment in MS pathogenesis are debated (Sawcer, 2011; Taylor, 2011). Perhaps the most compelling evidence in this regard has been the virtual epidemic of autoimmune and allergic disorders, including MS, in the developed world during the last century (currently approximately 50% for allergic and 3–5% for autoimmune disorders) (Bach, 2002; Cooke, 2009; Okada et al., 2010; Bilbo et al., 2011). This rise is too rapid for significant genomic alterations to occur and therefore implies that there has been a critical environmental change in