

Discussion paper

Managing multiple sclerosis in primary care: are we forgetting something?

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ABSTRACT

Multiple sclerosis (MS) is the commonest debilitating, progressive neurological disorder in most Western countries. It is important for many reasons, including the personal costs, levels of disability produced, age group affected and the resultant economic burden placed on individuals, families and the community. Although it is thought to be an autoimmune condition, in general little is understood about the causation of MS and the factors that trigger or contribute to exacerbations and deterioration. This overview of the literature will consider some important studies examining the relationship between lifestyle and psychosocial factors and MS progression. These studies suggest that nutrition, sunlight, exercise, stress and social factors can all modulate the rate of progression of MS and the level

of disability. Although appearing in respected journals, this information tends to be little known or discussed by clinician and patient alike. If lifestyle approaches do offer potential avenues for therapy, this raises important questions regarding the management of MS in primary care. More widely prescribed conventional medicines have been studied in more detail but are only modestly effective and may have significant side-effects. Are we presently neglecting the most effective approach of combining the non-drug or holistic approach with the best of conventional pharmaceutical therapies, and if so what are the implications of this omission?

Keywords: diet, exercise, holistic medicine, multiple sclerosis, sunlight, vitamin D

How this fits in with quality in primary care

What do we know?

Multiple sclerosis (MS) is an incurable, progressively disabling neurological disorder. We know that immunomodulatory disease-modifying therapies have only a modest effect on relapse rate, and even less effect on progression of disability. Most patients are offered these therapies at or soon after diagnosis. There is also, however, a comprehensive, highly persuasive literature on a variety of lifestyle and psychosocial factors that not only improve quality of life, but, in the available clinical studies, slow progression of the disease. These lifestyle therapies are not often employed in primary care management of MS.

What does this paper add?

Evidence from basic science, epidemiology and clinical trials now strongly supports an important role for lifestyle modification in managing MS in primary care. A very low saturated fat diet, essential fatty acid supplementation, adequate exposure to sunlight or vitamin D supplementation, stress management with techniques such as meditation, and regular exercise, in combination with the best of medical management, offer the best potential for significantly slowing the progression of this disease. These interventions are well suited to institution and continuing management by general practitioners with appropriate community support. The framework we outline provides an opportunity to maximise the quality of primary care management of MS.

The doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet, and in the cause and prevention of disease. (Thomas Edison)

Introduction

Multiple sclerosis (MS) is the most common neurological condition in young adults in developed countries. Despite decades of research, little is definitely established about its aetiology or triggering factors. Environmental factors play the major part in its incidence and expression, despite there being a clear genetic predisposition. There has been considerable research into non-drug therapies such as diet, sunlight, exercise and positive psychosocial support, yet conventional medicines alone are often the only treatment prescribed. This article examines the rationale for broadening therapy in MS in primary care using a more holistic approach utilising non-drug therapies, and discusses issues raised by their under-utilisation.

The role of nutrition

As Ornish was publishing his groundbreaking research in the holistic management of heart disease (including a low-fat diet, exercise, stress reduction and stopping smoking),¹ research from Canada was being published in *The Lancet* and elsewhere on a dietary intervention for the management of MS.^{2,3} The results were possibly even more startling, but received relatively little notice in the wider medical community. Swank found that over a 34-year follow-up only 31% of MS patients adhering to a low saturated fat diet (less than 20 g/day) died, compared with approximately 80% of patients not sticking to the diet.^{2,3} Furthermore, in the group who started with a lower level of disability only 5% had died. The rates of disease progression and disability were also vastly different in the two groups; 'when those who died from non-MS diseases were excluded from the analysis, 95% survived and remained physically active'.²

Perhaps the great strength of this study, its 34-year duration, also proved its great weakness. It was begun in 1949 when an uncontrolled observational cohort study was an accepted benchmark for testing a new therapy, but finally published in an era where standards of medical evidence had changed dramatically. An accompanying anonymous editorial in *The Lancet* was thus lukewarm, stating that 'the role of lipids in MS must remain not proven', and the therapy was largely ignored, despite the size of the effect, its otherwise

positive health benefits, and its enormous potential for the treatment of an 'incurable' disease.⁴

Fitzgerald and co-workers in the UK also studied the role of nutrition in MS. They showed that patients who adopted a similar diet did not worsen significantly over 34 months compared with those who did not.⁵ In other trials it has been found that supplements with essential fatty acids, particularly omega-3 fatty acids, are associated with significant reductions in the frequency and severity of relapses.^{6,7}

It has been well known for some time that fish and flaxseed oils have significant anti-inflammatory properties in a range of conditions including MS. Supplementation with fish oil in MS patients produces a degree of immune system modulation equivalent to some chemotherapy agents.⁸ These studies reinforce the findings of large-scale epidemiological studies and case-control studies suggesting strong links between animal fat consumption and MS incidence, an inverse relationship with fish consumption, and a protective role for vegetable-based diets.⁹⁻¹²

Plausible mechanisms have been proposed to explain these findings. There has been a long-known association of MS with cow's milk consumption.¹³ Recent high-quality basic research has provided an immunological basis. A number of cow's milk proteins were targeted by the immune cells of people with MS.¹⁴ Further injecting them into experimental animals caused lesions to appear in the central nervous system of the animals.¹⁵ Upregulation of lymphocyte apoptosis has been proposed as a possible mechanism for these dietary influences.¹⁶ Review articles are now beginning to paint a coherent picture.¹⁷

The role of sunlight and vitamin D

From consistent and reliable epidemiological data, countries with lower levels of sunshine have significantly higher incidences of MS.^{18,19} The overall incidence of MS in Australia is 13.5 per million for women and 7.7 for men, but the incidence varies six to sevenfold from Queensland to Tasmania.²⁰ In countries near the equator, MS is nearly unknown, whereas in very northern countries such as Denmark the incidence can be as high as 48.6 per million for women and 43.0 for men.²¹ This is likely to result from generation of vitamin D, a potent immune modulator.

Over an 11-year period, the odds ratio (OR) for death from MS was nearly halved (OR: 0.53) for those with higher residential sun exposure.²² High residential exposure and occupational exposure combined was associated with an odds ratio of 0.24. Australian data have shown that sunlight exposure correlates inversely with MS incidence even more closely than its direct correlation with melanoma.²³

Tasmanian data show that higher sunlight exposure between the ages of 6 and 15 years, particularly winter sun, resulted in an odds ratio of having MS in later life of 0.31.²⁴ Low levels of vitamin D have been strongly associated with more aggressive MS,²⁵ but until recently there have only been small-scale trials suggesting that vitamin D supplements can reduce MS exacerbations.^{26,27} It has been shown that seasonal variation in vitamin D levels inversely correlate with number of MS lesions on magnetic resonance imaging (MRI). The authors of this article recommended year-round supplements of 3000–4000 IU per day of vitamin D,²⁸ although in most places in Australia it is easy to get the small amount of sunlight exposure required to keep vitamin D levels high. Roughly 10–15 minutes of sunlight to most of the body on a day with UV index 7 produces 10 000 IU of vitamin D, and optimal immune system modulation. A very recent large-scale prospective cohort study has confirmed that even modest regular vitamin D intake (risk ratio (RR) 0.67; 95% confidence interval (CI) = 0.40 to 1.12; *P* for trend = 0.03) and vitamin D supplements of only 400 IU or more per day (RR 0.59; 95% CI = 0.38 to 0.91; *P* for trend = 0.006) were both associated with significantly lower risk of developing MS.²⁹

A recent prospective dose-escalation study examined the safety of higher-dose vitamin D supplementation.³⁰ Researchers gave increasing doses of the hormone to 12 people over 28 weeks, increasing the dose from 4000 IU per day up to 40 000 IU per day. Measured levels of vitamin D in the blood of these people were very high, much higher than what has been previously regarded as toxic, with average levels increasing to around 400 nmol/l. Despite these levels, no patient developed high calcium levels or any side-effects. It is interesting to note that the mean number of new MS lesions more than halved over the short period of the study, from 1.75 to 0.83 (*P* = 0.03). It is clear that supplementation with vitamin D at quite high doses is very safe, and the way is now clear to use larger doses of the order of 5000–10 000 U in research situations to examine the effect on relapse rates and disease progression.

The benefits of sunlight may also be due to the direct effects of sunlight on immune function and melatonin levels,³¹ as well as the indirect effects on vitamin D.³² Obviously, messages about the positive effects of sun exposure need to be given with messages about avoiding sunburn and over-exposure.

Psychosocial factors

Many psychoneuroimmunological mechanisms might explain relationships between psychological states,

immunity and autoimmune conditions.³³ For example, those who have higher sympathetic nervous system reactivity to stress (including increased blood pressure, heart rate and catechol hormones related to adrenaline) also have the greatest disturbance to immunity.³⁴ Furthermore, during high-stress periods there is a shift towards the type-2 response, which may partially explain the increased incidence of type-2-mediated conditions (e.g. infections, latent viral expression, allergic conditions and, importantly, autoimmune conditions) during high-stress periods. This inappropriate response is called immune ‘dysregulation’.³⁵ Stressful life events and unsupportive social environments are associated with the onset and exacerbation of a variety of autoimmune diseases.³⁶ Stress is also known to have significant effects upon hormones like tumour necrosis factor (TNF- α), a significant prognostic factor for MS.³⁷

Much of this is of clinical and not just theoretical relevance to primary care physicians. Recent research shows that psychological health has a significant impact upon the progression of MS as well as affecting how one copes with it. Depression and anxiety are very common among MS patients, and it is important to control these as part of supportive care, but their role in influencing clinical outcomes has possibly been underestimated. One trial showed that MS ‘exacerbations were more likely during at-risk periods following (stressful) life events and were relatively independent of the threat level and type of stressor’, particularly for people with a high degree of physiological reactivity to stressful events.³⁸ This has been confirmed in other studies examining MRI evidence of new lesions in the central nervous system, where stress was significantly related to the development of new brain lesions 8 weeks later (OR = 1.62, *P* = 0.009). Positive coping strategies were associated with a reduced number of brain lesions.^{39,40}

Recent reviews increasingly point to the importance of the mind in MS progression. ‘Chronic psychosocial stressors, however, such as interpersonal conflicts, loss and complicated bereavement, low perceived social support, anxiety and depressive episodes have to be regarded as possible risk factors for the development of MS exacerbations.’⁴¹ MRI and experimental studies, supporting the important role of nervous and immune system interactions, demonstrate a significant correlation between stress and MS exacerbations.⁴² Plausible mechanisms are being examined, although there are many questions still to be answered.⁴³ Levels of interferon, the principal medical treatment for MS, can be endogenously modulated with psychological methods (self-hypnosis or meditation), with beneficial side-effects,^{44,45} but the clinical significance is uncertain. Unfortunately, there is far less economic incentive to investigate this more ‘natural’ physiological therapy. The therapeutic potential for psychosocial

intervention altering the clinical course of the disease is largely untested as yet. Although such interventions will help patients cope with MS, it behoves the clinician to advise patients that undertaking psycho-social therapies as a routine part of their management plan may actually improve their clinical outcome. Such interventions will obviously need to be tailored to individual patient needs, insight and motivation.

Exercise

Exercise is of immense importance for MS patients in terms of maintaining strength, balance, function and general fitness, as well as having a positive role in mental health and social interaction.⁴⁶ The SWEAT (Sutherland Water Exercise and Activity Training) hydro-therapy programmes run by the MS Society in Victoria have been shown to be associated with improved quality of life,⁴⁷ and other studies have shown their effect on reducing depression,⁴⁸ which is known to be associated with an adverse immune system cytokine profile in MS. The role of exercise in reducing the number or severity of MS exacerbations has not yet been sufficiently examined. A 2008 review of the literature concluded that:

... evidence exists for recommending participation in endurance training at low to moderate intensity, as the existing literature demonstrates that MS patients can both tolerate and benefit from this training modality. Also, resistance training of moderate intensity seems to be well tolerated and to have beneficial effects on MS patients ...⁴⁹

Regular aerobic activity is required to maintain the benefits.⁵⁰

Discussion

Overall, there is presently enough evidence for lifestyle therapies to be a standard part of the primary care management of MS, although advice about better outcomes needs to be realistically founded on the best available evidence. However, an increasing number of patients take these issues into their own hands; 64% of German patients with MS are using complementary and alternative medicine (CAM),⁵¹ and the figure in Australia is probably comparable. Many people, especially with chronic illnesses, are turning to CAM practitioners for non-drug therapies, a holistic approach and lifestyle advice, because they perceive, rightly or wrongly, that CAM practitioners have the greater time, skills and inclination to provide such care than their general practitioners (GPs). What is being

advocated in this article is not the use of CAM *per se*, but rather the use of lifestyle strategies that should underpin any comprehensive medical care. Studies suggest that patients adopting CAM do it not because they wish to reject conventional medicine, but to augment it because by itself it is perceived as being incomplete.^{52,53} Other concerns include the cost and side-effects of conventional medical treatments.

It is unfortunate that many patients perceive the need to go outside the primary healthcare system to get such help, but gathering evidence suggests that this desire may be well founded. Furthermore, many patients will not tell their doctors that they are seeing other therapists, which raises important questions about doctor–patient trust, communication and safe monitoring. Doctors must surely be concerned that patients receive the most balanced, up-to-date and reliable information possible. Many people are searching for the advice from complementary practitioners which they should possibly be receiving from their GPs. Given that these non-drug therapies are likely to be associated with other positive health outcomes, there are good reasons to recommend them. It is likely for instance that a low saturated fat diet and adequate sunlight protect against a range of Western diseases including various cancers, degenerative diseases and autoimmune diseases.

Despite accumulating evidence regarding lifestyle, diet and psychological factors, as summarised in Table 1, these rarely form a significant part of the management of MS, which tends to rely on heavily promoted conventional medicines, despite their modest effects, side-effects, and methodological concerns about the clinical trials. The medical therapy most widely propagated is interferon beta,⁵⁴ which has mostly short-term evidence showing that it reduces the number of relapses by perhaps 30% although ‘one-third of patients experienced a higher or identical annual relapse rate while on IFNB [interferon beta] treatment’.⁵⁵ This has to be balanced against the enormous financial cost and, more importantly, the significant side-effects including ‘flu-like symptoms’, such as major levels of malaise and lethargy because of its effects as an immune system modulator, and other more serious effects. These symptoms often have to be controlled with a variety of medications with their own side-effects. A recent meta-analysis of the interferon studies for MS highlighted that as well as being relatively short term (the effect beyond 12 months was unproven), the studies were in effect unblinded as most participants easily guessed whether they were on the drug, due to side-effects. There has also been a high dropout rate, and where this has been analysed, patients dropping out have had poor responses to treatment.⁵⁶ Another compound showing promise, glatiramer acetate (Copaxone-Teva), has fewer side-effects and similar benefits but is less widely used.^{57,58} Although comparisons

Table 1 Lifestyle and psychosocial factors probably influencing the progression of multiple sclerosis

Negative factors	Positive factors
Nutrition: High animal (saturated) fat Dairy products Low vitamin D intake	Nutrition: Very low animal (saturated) fat No dairy products Omega-3 fatty acids (e.g. fish, flaxseed oil) Vitamin D (3000–4000 units per day)
Lack of sunlight	Minimal regular sunlight exposure (10–15 minutes exposure of most of body surface 2–3 times a week)
Psychosocial stress	Positive mental and social health and coping strategies
Inactivity	Exercise

are as yet difficult to quantify, the size of the clinical effect with these current disease-modifying drugs may be many-fold less than that reported with diet, let alone a combination of non-drug therapies.

Many other important issues for debate are raised by the above considerations. The non-drug approach to MS highlights the potential role for holistic lifestyle therapies for chronic disease and is echoed in other programmes like the lifestyle approach to treating heart disease investigated and now shown by Ornish and colleagues to produce sustained benefit.⁵⁹ Promising results of their programme are now also being seen in the treatment of prostate cancer. Two years into this study, only 5% of patients with prostate cancer who had adopted the lifestyle approach required conventional medical treatment for the cancer, compared with 27% of those on standard therapy.⁶⁰ There looks to be enormous potential for better therapeutic outcomes in quality of life, disease progression and reduced healthcare costs by such an approach.⁶¹

The lifestyle approach in primary care, especially for chronic illness, should be first-line therapy and not an afterthought. The slowness in adoption of this approach needs to be examined. In contrast, there is a tendency to readily embrace heavily promoted drug treatments with their associated high cost and frequent side-effects, despite concerns regarding supporting evidence and patient quality-of-life issues. Importantly, however, a holistic approach is not an argument against the judicious and appropriate use of pharmacological and technological advances. A balanced approach in primary care uses the best that every therapeutic modality has to offer.

Larger and longer-term outcome trials are methodologically difficult to perform but are an important final arbiter of effectiveness, but while we await the results of such trials, present evidence supports the use of non-drug therapies. If the orthodox healthcare

system does not embrace a more holistic approach to the prevention and treatment of many diseases, there will be a continuing and understandable movement towards CAM practitioners. Furthermore, as more evidence is gathered, there are growing potential medicolegal and economic implications in not recommending lifestyle and holistic therapies.

Who should implement such treatment options? Specialists certainly have a central role in the recommendation of these therapies, although due to time and training they may feel less inclined to be the ones to implement these lifestyle and psychosocial strategies. This role may be better suited to the GP or other suitably trained allied health professional who can work in conjunction with specialist care. Perhaps some of these holistic interventions can be best delivered through MS support groups, the MS Society and other community support programmes. Although some aspects of these strategies may be more time intensive initially, with a chronic and potentially debilitating disease like MS the long-term clinical, time and resource benefits are likely to be strongly positive.

Conclusion

There is a pressing need for education about and implementation of lifestyle strategies for the standard management of MS. This needs to be in conjunction with the judicious use of evolving medical therapies. This education and implementation needs to involve GPs and students, MS patients and carers, allied health professionals, and consumer and advocacy groups involved with the care of people with MS. This appears to be the most sound and effective way to enhance care and outcomes.

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PEER REVIEW

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CONFLICTS OF INTEREST

Professor Jelinek was diagnosed with multiple sclerosis in April 1999.

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