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Factors associated with onset, relapses or progression in multiple sclerosis: A systematic review

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ABSTRACT

Multiple sclerosis (MS) is a chronic disease of the central nervous system with an unidentified etiology. We systematically reviewed the literature on the possible risk factors associated with MS disease onset, relapses and progression from 1960 to 2012 by accessing six databases and including relevant systematic reviews, meta-analyses, case-control or cohort studies. The focus was on identifying modifiable risk factors. Fifteen systematic reviews and 169 original articles were quality assessed and integrated into a descriptive review. Best evidence, which included one or more prospective studies, suggested that lower exposure to sunlight and/or lower serum vitamin D levels were associated with an increased risk of developing MS onset and subsequent relapses, but a similar quality of evidence was lacking for disease progression. Prospective studies indicated that cigarette smoking may increase the risk of MS as well as accelerate disease progression, but whether smoking altered the risk of a relapse was largely unknown. Infections were implicated in both risk of developing MS and relapses, but data for progression were lacking. Specifically, exposure to the Epstein-Barr virus, particularly if this manifested as infectious mononucleosis during adolescence, was associated with increased MS risk. Upper respiratory tract infections were most commonly associated with an increase in relapses. Relapse rates typically dropped during pregnancy, but there was no strong evidence to suggest that pregnancy itself altered the risk of MS or affected long-term progression. Emerging research with the greatest potential to impact public health was the suggestion that obesity during adolescence may increase the risk of MS; if confirmed, this would be of major significance.

1. Introduction

Multiple sclerosis (MS) is a complex neurological condition characterized by inflammation, demyelination and axonal degeneration of the central nervous system. It is considered the most common cause of neurologic disability among young adults in the West (Leary et al., 2005). Approximately 1.3 million people are affected worldwide (WHO, 2008). North America, Europe and Australasia have moderate to high rates of MS, with around 1–2 people per 1000 affected (Evans et al., 2013). MS incidence typically peaks around 30 years of age, with more women than men affected (Marrie et al., 2010b). The high prevalence in conjunction with the relatively young onset age and the chronic nature of MS translates into higher societal costs than either stroke or Alzheimer's disease (Pugliatti et al., 2006).

Although many factors – including genetic and environmental – have been implicated in either triggering MS or modulating the subsequent disease course, results vary substantially between studies. Few systematic reviews consider more than one risk factor at a time, such that it is hard to establish a comprehensive understanding of the (likely) multiple risk factors involved in modifying MS risk. In addition, few risk factors have been successfully targeted or modified in order to reduce the risk of developing MS or delay disease progression (drug treatments aside). Further, the literature surrounding risk factors associated with onset or disease progression in MS has grown rapidly over the last few decades. Therefore there is a real need to understand the broad range of risk factors linked with MS and the level of evidence associated with these factors.

This systematic review of the literature aimed to integrate findings on risk factors that might influence the onset of MS or MS disease activity (relapses or progression).

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2. Methods

This review was conducted using a centralized protocol designed by the University of Ottawa, Canada's National Population Health Study of Neurological Conditions project and adapted to study MS. Key points and adaptations are summarized here:

2.1. Inclusion and exclusion criteria

To be included in this systematic review articles had to be original observational studies (case-control or cohort), systematic reviews, or meta-analyses that examined at least one risk factor associated with the onset and/or disease activity (relapses or progression) in MS. Only studies that reported a quantifiable measure of risk, involved human subjects, and were published in English or French were included.

Articles were excluded on any of the following grounds: did not specifically assess risk factors, e.g. studies which examined biomarkers for diagnostic purposes; did not analyze or report quantitative data e.g. were predominantly descriptive; the risk factor under review was a form of intervention or pharmacological treatment for the disease or part of a randomized controlled trial designed for a therapeutic intervention. An exception was made for studies occurring within a clinical trial or making secondary use of the clinical trial data and only when the exposure of interest was unrelated to the therapeutic intervention. No restriction was imposed in terms of age, sex, race, geographical residence, or source of population of participants (e.g. community, hospital, outpatient, registry or health administrative data).

Outcomes of interest were: MS onset and disease activity (relapses or progression). MS onset was typically considered as the first symptomology related to subsequent diagnosis of MS. Ideally MS diagnosis would involve internationally-recognized criteria (e.g. Schumacher, Poser, or McDonald), although studies using other methods (e.g. health administrative data or self-report) were considered. There is a large body of research describing the risk of reaching a diagnosis of MS in special subgroups of patients, e.g. those with optic neuritis or other clinically isolated syndromes. These studies were considered beyond the scope of this review and were not included.

MS disease activity is multifaceted and variable and for the purposes of this review, we considered clinical relapses ('attacks') and disease progression. MS relapses (acute worsening of function followed by partial or complete recovery) were considered a measure of short-term disease activity. Studies measuring longer-term disease activity, i.e. progression were also included, regardless of what measure(s) were used. The Expanded Disability Status Scale (EDSS) is a 20-point scale (ranging from 0 = normal to 10 = death due to MS, marked by 0.5 increments) and is currently the most widely used measurement (Kurtzke, 1983). It is an expansion of the Disability Status Scale (DSS), which applied the same range, without the 0.5 increments (Kurtzke, 1955). The transition from relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS) is also often used as a measure of progression, typically recognized clinically as 'progression with or without occasional relapses, minor remissions, and plateaus.' We did not include studies that focused on death ('all-cause mortality') as an outcome, nor did we include studies reporting the association between our defined outcomes e.g. between relapses and progression. All risk factors (other than interventions) were considered, although our primary focus was on factors most amenable to modification, i.e. with the potential for the highest public health impact. Demographic factors, such as age and sex were not a major focus. For example, it is generally well established that age and sex influence MS risk. This information is best represented in incidence/prevalence studies which are being comprehensively covered in a separate series of systematic reviews funded in the same cycle as this current review (Evans et al., 2013; Kingwell et al., 2013). These studies are also well-suited to examine the possible influence of latitude in relation to MS risk; therefore latitude was not covered here. Genetic risk factors associated with MS disease activity (relapses or progression) were systematically reviewed; however, genetic factors associated with MS risk were considered beyond the scope of this review. Instead, findings from a credible and comprehensive field synopsis of published genetic association studies, MSGene, were summarized (Lill et al., 2013). Finally, the vast topic on the prognosis of MS (often termed 'the natural history of MS') was not systematically re-reviewed here, rather a brief overview was provided.

2.2. Search methods for identification of study scope

Firstly, a search strategy was developed using MeSH terms in MEDLINE (OvidSP) as well as relevant keywords. Subject headings explored in OvidSP were inclusive of "multiple sclerosis", "disseminated sclerosis", "chronic progressive", "acute fulminating relapsing" and "remitting". Synonym mapping, and scope notes in MEDLINE were used to identify the appropriate subject headings. All the relevant words (e.g. sclerosis), phrases (e.g. multiple sclerosis) or a combination were used. All possible synonyms (e.g. acute versus severe), alternate terminologies (e.g. disseminated sclerosis versus multiple sclerosis), variant word endings (sclerosis versus multiple) were also adopted. No alternate spellings were required. Boolean logic was used to combine concepts and drop irrelevant articles.

Secondly, the following broader MeSH terms were added to the search: "risk factor", "odds ratio", "relative risk", "risk difference", "predictor" or "prediction" or "predisposition" and "progression". Keywords adopted from other search strategies of relevant studies were added to the current search.

The search for relevant publications was carried out in two stages; the first focused on identification of systematic reviews and/or meta-analyses, the second on original observational studies. The original search was conducted in May 2011 and then updated to the end of May 2012 for original articles, and December 2012 for systematic reviews/meta-analyses. This lag-time enabled the most recent systematic reviews to be included, thereby maximizing the number of studies included, whilst balancing time and resources which prevented an update on our search for original articles to the latter date. The following databases were searched from their respective initiation (year shown in brackets): MEDLINE (1996), Cochrane Central Register of Controlled Trials (1991); EMBASE (1980); CINHAL (1982), PSCYINFO (1990), AGELINE (1982). Searches were completed via OvidSP, and EBSCO. To minimize the possibility of a missed article, references of retrieved articles were checked and experts in the field were approached to critique early drafts of the review (see acknowledgements). These resources were considered as 'additional' records. Detailed search strategies are provided in the Supplementary material I.

2.3. Article collection, screening and data extraction

Articles were initially stored in Endnote®, a reference manager, and duplicates were deleted. The remaining articles were transferred to Distiller®; an online application designed to facilitate literature screening and data extraction. Articles were screened at three levels: title, abstract, and full paper.

Article titles were assessed and either excluded or promoted by two reviewers (stage 1a). Abstracts of all potentially relevant articles were then retrieved and screened in a similar manner (stage 1b). Cohen's kappa coefficient for the level of agreement for