Multiple Sclerosis and Related Disorders 14 (2017) 56–59

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Infectious mononucleosis and multiple sclerosis – Updated review on associated risk

Sharaf Sheik-Ali

Barts and the London School of Medicine and Dentistry, United Kingdom

ARTICLE INFO

Keywords:
Infections
MS
Multiple Sclerosis

ABSTRACT

Background: There has been substantial evidence accumulating on the role of infectious mononucleosis (IM) and the subsequent risk of obtaining Multiple Sclerosis (MS). Up to date studies not previously explored were reviewed by the author to further clarify the association.
Methods: Medline and Web of Science were searched with no time constraints for articles exploring an association between Multiple Sclerosis and Infectious Mononucleosis. 24 articles were found, totalling 1063 cases and 13,227 cohort/controls.
Results: 23/24 (96%) articles reported a significant association of Infectious Mononucleosis on the risk of subsequent multiple sclerosis.
Discussion: Overall, new literature on IM and risk of MS categorically supports the association. Future work should focus on other risk factors such as age and gender on IM and subsequent risk of MS.

1. Introduction

Multiple Sclerosis is a progressive, chronic neuro-inflammatory disease characterised by demyelinating lesions of the Central Nervous System (CNS). Clinically, MS is diagnosed by two or more CNS lesions separated by time or space. To date, significant strides have been made in MS research since the first diagnosed case in the early nineteenth century. However, there is still considerable work to be done to understand the complete aetiology of the condition.

MS commonly presents as an acute unilateral optic neuritis, often associated with numbness or weakness of the lower limbs. Symptoms can vary from mild visual disturbances to hemiparesis and paralysis. Prognosis is significantly worsened in late presentations of MS in patients with a history of symptomatic fluctuating episodes.

Clinical presentation and MRI imaging are the first means of diagnosis that are supported further by oligoclonal bands present in the CSF, detected via electrophoresis. Requirements include lesions disseminated in time and space, with no known cause (Goldenberg, 2012)

Currently there is no cure. Treatment aims to reduce the number of relapsing episodes, slow the progression and improve the quality of life that is inevitably worsened by disability. Immunosuppressive agents such as azathioprine, monoclonal antibodies such as alemtuzumab and steroids; typically methylprednisolone, are often used to control disease progression (Goldenberg, 2012).

There has been an accumulation of case control and cohort studies that show an association between Multiple Sclerosis (MS) and Epstein Bar Virus (EBV) (Pakpoor, 2016). EBV can either present asymptomatically or symptomatically, the latter as a lymphoid infection known as infectious mononucleosis (IM) (Henry and Balfour, 2015). It is currently known that both IM and MS usually occur in a younger age group and both follow the same latitude gradient, which is suggestive that it is perhaps IM that has a greater association with MS.

The association of IM to MS is well explored in the literature, here I provide an up to date review with the inclusion of new studies not included in previous reviews on the risk of IM and MS.

2. Methods and search criteria

A literature search was conducted electronically in Medline with no time constraints using "(*Infectious Mononucleosis*", "*Epstein-Barr Virus*)" AND "(*Multiple Sclerosis*)", including mesh terms with no language restrictions. A similar search was conducted via web of science, using the following search criteria; "(*MS" or "Multiple Sclerosis" or "disseminated sclerosis" or "encephalomyelitis disseminate*)" AND "(*infectious mononucleosis" or "glandular fever" or "EBV" or "Epstein–Barr virus*" or "human *herpes virus 4*" or "*HHV-4*" or "*Pfeiffer's disease*)" as key words.

2.1. Inclusion criteria

- Epidemiological study (cross-sectional, case-control, cohort study)

E-mail address: sharaf554@gmail.com.

http://dx.doi.org/10.1016/j.msard.2017.02.019
Received 27 December 2016; Received in revised form 20 February 2017; Accepted 25 February 2017

- Diagnosis of MS (definite/probable)

2.2. Exclusion criteria

- Studies on non-human subjects.
- Non-Epidemiological studies
- Not relevant to the topic

The exclusion criterion was kept to the minimal to generate a wider search. Abstracts were read in order to select cohort/case-control or cross-sectional studies. Data was extracted from full texts of selected articles consisting of: odds ratios or relative risk. Information was also extracted on outcome and MS definition, median age of IM infection, F/M ratio and MS type.

3. Quality assessment

The Newcastle Ottawa Assessment Scale (index 1-original version) to assess the quality of each accepted paper. Categories were divided into selection, comparability and outcome measure. Each article could score a maximum of 4 in selection, 2 in comparability and 1 in outcome measure.

The selection criteria had four different scores available for articles that conformed to each requirement. This criterion had the primary aim of identifying articles that had clear defined cases and controls that were representative of the population. A “4/4” scoring article for instance, would have the number of cases and controls, how they were selected out of a given population and any measures the authors took in recruiting participants.

The comparability criteria aimed to identify articles that had as close matched cases and controls as possible. This would significantly reduce effects of variables and risk factors for multiple sclerosis such as differences in smoking exposure. The first available point was given to articles that “controlled at least two variables between cases and controls”. This was typically previous history of medical conditions and area participants grew up in. 2 points in this section would suggest that the only difference between cases and controls was IM exposure, and groups were matched almost identically; i.e age, gender and exposure risks.

Outcome assessment aimed to highlight those articles that had recorded not just how multiple sclerosis was diagnosed, but also the type of MS controls developed. This data could potentially enable us to understand the pathophysiology behind the association. Articles scored a maximum of 1 in outcome assessment.

The total was calculated by adding the respected Section 4 was the highest score available for selection, 2 for comparability and 1 for outcome assessment. Therefore, the articles were scored out of a possible 7. This is demonstrated within the results section.

4. Results

In total, after removing duplicates, 912 articles assessing the association between infectious mononucleosis and multiple sclerosis were identified. To avoid missing any papers that may have been relevant to this topic, references were examined of relevant articles and an additional 5 studies Ire included. After selecting papers that were in keeping to the inclusion criteria, assessing their eligibility to the study and scrutinizing their experimental methods, a total of 24 articles were identified. These comprised of 5 nested case control studies, 10 population based case control studies, 6 hospital record case control studies and 2 case control studies that Ire not specified. The search is demonstrated in the below flow diagram. Fig. 1 and Table 1

Overall, this gave produced a participant number of 1063 cases and 13,227 cohort/controls. The median size of cases was 145 and 165 controls respectively. Flowchart 1

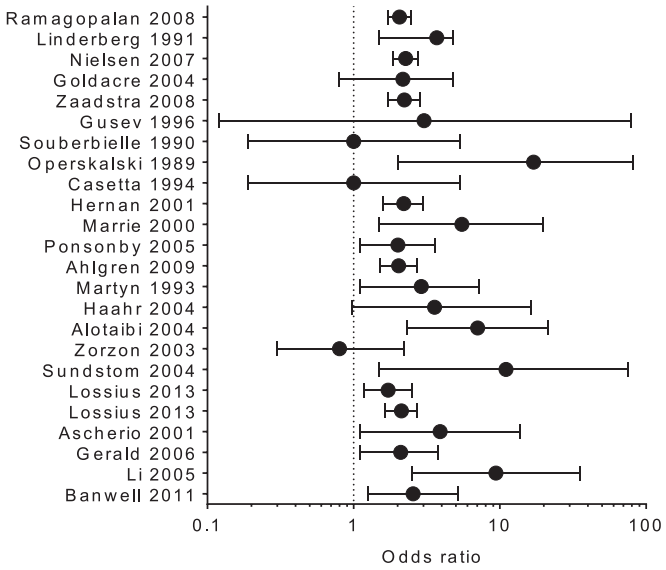

Fig. 1. Forest plot depicting Odds ratio's of IM and MS association.

4.1. Studies design

The nested case controls enlisted participants who had their serum samples stored before developing multiple sclerosis. Participant's serum was analysed for EBNA or VCA antibodies; antibodies that can be used in IM diagnoses. I used the reported odds ratio of obtaining MS from participants who were positive for EBNA or VCA antibodies when matched to their controls.

The population and hospital based case control articles studied exposure risks in patients diagnosed with MS. The majority of studies followed a format of using questionnaires to assess if participants had previously had infectious mononucleosis. Other studies had participants antibodies (provided through blood samples) checked for specific antibodies prevalent in IM. For instance, Lossius et al. (Lossius et al., 2016) in 2013 opted for an EnvIMS-Q (Environmental risk factors in multiple sclerosis) questionnaire in which participants recorded previous IM infection, whereas Sundstrom et al (Sundström et al., 2016) in 2004 studied the serum samples of MS cases and analysed IgG antibody responses for EBNA-1 and VCA.

5. Discussion

The number of studies reporting a positive association between infectious mononucleosis and multiple sclerosis was 96% (23 of the 24 studies). With the inclusion of up to date studies, I add further support to the increasing consensus that IM can increase MS risk.

The odds ratio's showed a unanimous positive association between IM and MS. Odds ratios ranged from 0.8 to 17 respectively with the majority (20) reporting a significant result. Only one study, (Zorzon et al., 2016), showed no association between the two conditions. However, the authors still concluded with the possibility of an association and, due to the sample size, encouraged further studies to assess this.

A recent meta-analysis and systematic review of epidemiological associations of multiple sclerosis (MS) revealed evidential associations of infectious mononucleosis and anti-EBNA IgG seropositivity with MS (2·17, 1·97-2·39; p=3·1×10(−50); I(2)=0%) (Belbasis et al., 2017). Thus, alongside the results from this study, I add further up to date support to the hypothesis that IM has an association with MS (Thacker et al., 2017). However, although numerous studies report an association, the overall hypothesis attributing causality is weak. It is evident that of the 95% of the world population that acquire EBV infection, only a small proportion in high prevalence areas develop multiple