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Prevalence of Anti-JC Virus Antibody Seropositivity in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis

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Keywords
Multiple sclerosis · John Cunningham virus · Prevalence

Abstract
Background: The John Cunningham virus (JCV) is the causative agent of progressive multifocal leukoencephalopathy. Anti-JCV antibody seropositivity is an important consideration in patients with multiple sclerosis (MS). The reported prevalence of JCV in MS patients has been conflicting. ***Objective:*** We aimed to conduct a systematic review and meta-analysis to estimate the pooled prevalence of anti-JCV antibody seropositivity in cases with MS. ***Methods:*** We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, ProQuest, Google Scholar, and gray literature including reference of included studies, and conference abstracts which were published up to April 2019. Two independent researchers independently assessed the articles. ***Results:*** The literature search found 181 articles. After eliminating duplicates, reviews, case reports, and trials, 15 articles remained. Finally, 8 articles were included for the final analysis (from Asia, Europe, the USA, and Canada). In total, 16,041 MS cases were analyzed. The prevalence of anti-JCV antibody seropositivity varied between 40 and 80%, and the pooled estimate was calculated as 60% (95% CI: 56–64%), though with significant heterogeneity (I^2 = 95%, p = 0.01). ***Conclusion:*** The prevalence of anti-JCV antibody seropositivity is variable among MS patients in different countries, and the pooled estimate showed that this is 60% overall.

Introduction

The John Cunningham virus (JCV) is a common polyomavirus which can cause progressive multifocal leukoencephalopathy (PML), an infrequent lytic infection of glial cells [1, 2]. PML mostly occurs in immunosuppressed patients who have HIV infection or patients who have received immunomodulatory therapies including monoclonal antibodies (e.g., natalizumab, efalizumab, and rituximab) [3, 4].

Anti-JCV antibody seropositivity before natalizumab administration is considered an important risk factor for PML development in relapsing-remitting multiple sclerosis (MS) patients who are candidates for this treatment [5, 6]. Detection of anti-JCV antibody in serum by means of 2-step ELISA methods is possible which could help

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Table 1. Characteristics of included studies

First author	Published year	Country	Mean age, years	Mean duration of disease, years	Cases with anti-JCV antibody seropositivity	Total number of cases
Lau et al. [13]	2018	Hong Kong	36±12.9	5±1.6	98	123
Koolaji et al. [14]	2018	Iran	33.1±9.4	7.5±5.1	545	803
Kolasa et al. [15]	2016	Finland	40.9±10.4	6.9	233	406
Bhan et al. [2]	2014	Canada	44	12.3±9	2,363	4,197
Bozic et al. [16]	2014	Ten countries	43.2±11.4	11.6±8.8	4,410	7,724
da Silva et al. [17]	2014	Portugal	41.6±9.9	12.2±7.8	91	131
Lamdhade et al. [18]	2014	Kuwait	29.3±8.5	5.3±5	44	110
Bozic et al. [19]	2011	USA	–	–	1,305	2,547

identify patients who are at risk of PML [2]. In previous studies focusing on anti-JCV antibody seropositivity, the prevalence varied between 39 and 91% according to sample size, the geographical region, and age of patients [7–11]. As there is a wide discrepancy among the reported prevalence of anti-JCV antibody seropositivity in MS patients, we aimed to conduct this systematic review and meta-analysis to estimate the pooled prevalence of anti-JCV antibody seropositivity in MS patients.

Methods

Literature Search

We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, Google Scholar, and gray literature including references of included studies, and conference abstracts which were published up to April 2019.

Inclusion Criteria

1. Cross-sectional studies evaluating anti-JCV seropositivity in MS cases.
2. Articles which had been published in the English language.

Exclusion Criteria

1. Prospective or retrospective studies.
2. Anti-JCV antibody seropositivity in a specific group of cases.
3. Studies in which patients had been treated by disease-modifying treatment before anti-JCV antibody sera assessment.

Data Search and Extraction

The search strategy was as follows: ([JC virus] OR [JCV] OR [John Cunningham virus]) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR (Sclerosis, Disseminated) OR (Disseminated Sclerosis) OR MS (Multiple Sclerosis) OR (Multiple Sclerosis, Acute Fulminating). The retrieved articles were assessed by 2 independent researchers. Data on the total number of participants, first author, publication year, country, mean patient age, mean disease duration, and number of cases with anti-JCV antibody seropositivity were extracted from the included studies.

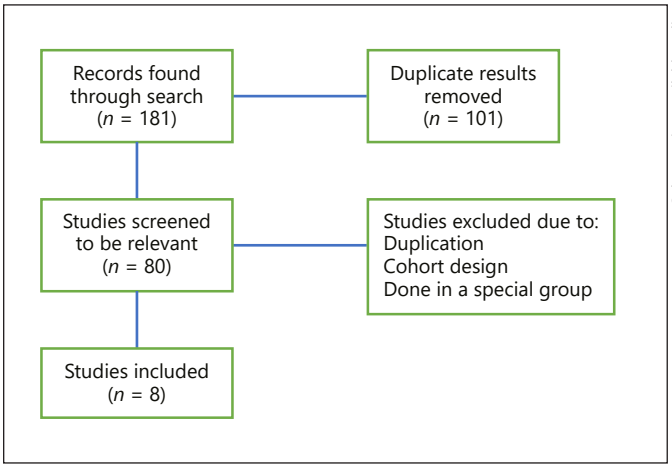

Fig. 1. Flowchart of included studies.

Risk of Bias Assessment

We evaluated the risk of potential bias by means of the Newcastle-Ottawa Scale (adapted for cross-sectional studies) [12].

Statistical Analysis

STATA (version 13.0; Stata Corp LP, College Station, TX, USA) was used for statistical analysis. We used the inverse variance with random-effects model. Heterogeneity was determined by means of inconsistency (I^2). In the Lau et al. [13] study, age was presented as median and interquartile range, which were transformed to mean and standard deviation.

Results

We found 181 articles after the initial search. After eliminating duplicates, reviews, case reports, and trials, 15 articles remained. Full-text evaluation resulted in the inclusion of eight articles for final analysis (Fig. 1). In total, 16,041 MS cases were analyzed (Table 1). The preva-

Table 2. Quality assessment of included studies

	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Outcome 1	Outcome 2	Score
Lau et al. [13]	A	a	B	a	–	b	A	7
Koolaji et al. [14]	a	a	B	a	–	b	A	7
Kolasa et al. [15]	a	a	B	a	–	b	A	7
Bhan et al. [2]	a	a	B	a	–	b	B	6
Bozic et al. [16]	a	a	B	a	–	b	B	6
da Silva et al. [17]	a	a	b	a	–	b	A	7
Lamdhade et al. [18]	a	a	b	a	–	b	B	6
Bozic et al. [19]	a	a	b	a	–	b	B	6

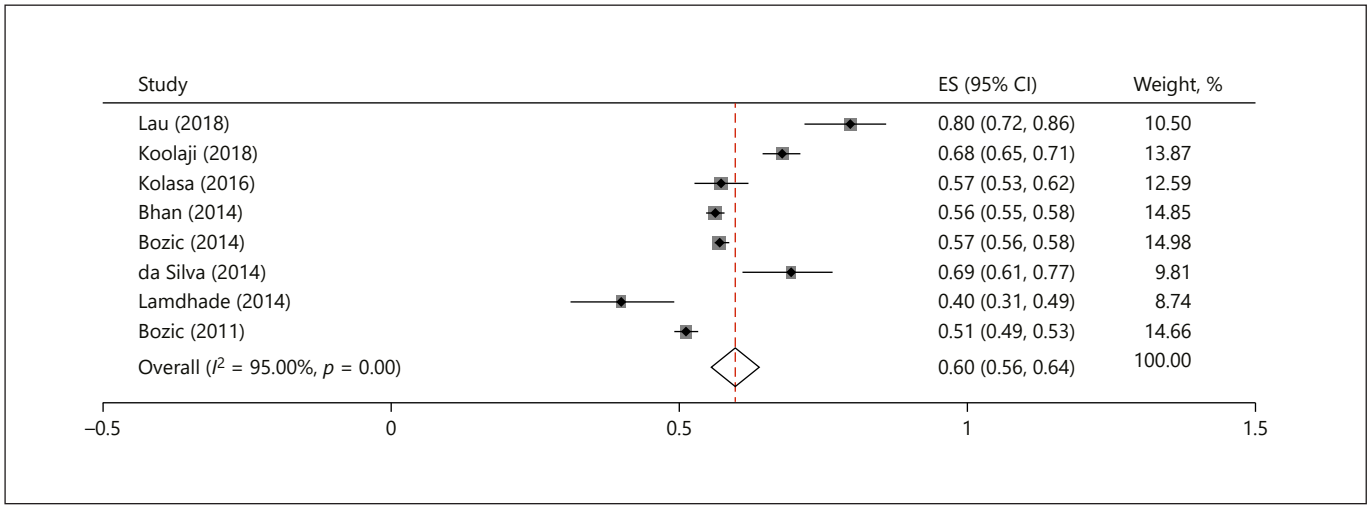

Fig. 2. Forest plot showing the result of pooled anti-JCV antibody seropositivity in MS patients.

lence of anti-JCV antibody seropositivity varied between studies from 40 to 80%, and the pooled estimate was calculated as 60% (95% CI: 56–64%), with significant heterogeneity (I^2 = 95%, p = 0.01) (Fig. 2). Quality assessment showed that all included studies had high quality (score 6 or 7) (Table 2).

Discussion

To our knowledge, this is the first meta-analysis to estimate the pooled prevalence of anti-JCV antibody seropositivity in patients with MS. The results demonstrated that the pooled estimate is 60%, while the prevalence varies from 40 to 80% in included studies which are from Asia, Europe, and the USA.

In the previous systematic review which was conducted by Paz et al. [20], the median prevalence of anti-JCV antibody seropositivity in MS and NMO cases was determined as 58%. We included only studies in which patients were not under treatment with monoclonal antibodies as some previous studies demonstrated that seroconversion occurs in patients who are under treatment with natalizumab [21, 22].

Schwab et al. [23] in a recent meta-analysis found that the mean seroconversion rate in natalizumab-treated MS patients was 10.80%, which means that consecutive evaluation of MS patients who are under treatment with natalizumab for anti-JCV antibody is required. Anti-JCV antibody status will guide physicians to continue or discontinue natalizumab for PML prevention [24]. On the other hand, antibody index value had been considered to be correlated with the risk of PML development [25]. The mechanism by which natalizumab could reactivate JCV in the CNS is not apparent [26].

By including patients from the Eastern Mediterranean, Alroughani et al. [27] investigated that age and male gender were associated with seropositivity of anti-JCV antibody. Koolaji et al. [14] reported anti-JCV antibody seropositivity in 67.9% of Iranian MS patients was correlated with age, male gender, disease onset age, and residing in cold areas. The mean age of seropositive cases in the Lamdhade et al. [18] cohort study of MS patients was significantly higher than that of seronegative cases (33 vs. 29.2 years).

Egli et al. [8] reported a prevalence of anti-JCV antibody in 58% of 400 healthy subjects (age 20–29 years) and 68% in older cases (50–59 years), which is in accordance with an Australian study finding [10]. In a Finnish study included in this systematic review, longer disease duration was not correlated with JCV seroprevalence, while they found that higher age and male gender were related to higher seroprevalence [15].

Unlike BK virus, the rate of JCV infection increases during life [7, 10], which could explain the higher prevalence in older MS cases. Olsson et al. [28] suggested that earlier treatment with disease-modifying treatments did not predispose the MS cases for anti-JCV seropositivity, which confirmed the Sørensen et al. [6] findings.

Conclusion

Prevalence of anti-JCV antibody seropositivity is discrepant among MS patients between different countries, and a pooled estimate showed that the prevalence is 60% overall.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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