Systematic review of the published data on the worldwide prevalence of John Cunningham virus in patients with multiple sclerosis and neuromyelitis optica

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OBJECTIVES: John Cunningham virus (JCV) is a polyoma virus that infects humans, mainly in childhood or adolescence, and presents no symptomatic manifestations. JCV can cause progressive multifocal leukoencephalopathy (PML) in immunosuppressed individuals, including those undergoing treatment for multiple sclerosis (MS) and neuromyelitis optica (NMO). PML is a severe and potentially fatal disease of the brain. The prevalence of JCV antibodies in human serum has been reported to be between 50.0 and 90.0%. The aim of the present study was to review worldwide data on populations of patients with MS and NMO in order to establish the rates of JCV seropositivity in these individuals.

METHODS: The present review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and used the following search terms: “JCV” OR “JC virus” AND “multiple sclerosis” OR “MS” OR “NMO” OR “neuromyelitis optica” AND “prevalence.” These terms were searched for both in smaller and in larger clusters of words. The databases searched included PubMed, MEDLINE, SciELO, LILACS, Google Scholar, and Embase.

RESULTS: After the initial selection, 18 papers were included in the review. These articles reported the prevalence of JCV antibodies in the serum of patients with MS or NMO living in 26 countries. The systematic review identified data on 29,319 patients with MS/NMO and found that 57.1% of them (16,730 individuals) were seropositive for the anti-JCV antibody (range, 40.0 to 69.0%).

CONCLUSIONS: The median worldwide prevalence of JCV among adults with MS or NMO was found to be 57.1%.

KEY WORDS: JC virus, Multiple sclerosis, Neuromyelitis optica, Progressive multifocal leukoencephalopathy, Natalizumab
tors in the body, it has proven to be very difficult to propagate JCV in human cell culture systems [1].

JCV can cause progressive multifocal leukoencephalopathy (PML), a severe disease of the brain resulting from the lytic infection of glial cells in immunosuppressed patients [6]. Management of this potentially lethal infection by rapidly restoring immune function may trigger another dramatic condition known as immune reconstitution inflammatory syndrome (IRIS) [7]. Although acquired immune deficiency syndrome was the main cause of PML for many years, the advent of very potent monoclonal antibody immunological treatments has brought about a new category of patients at risk of PML [8]. In neurology, the use of natalizumab for treating multiple sclerosis (MS) has led both to a remarkably efficient therapy and to a new severe adverse event [9]. The use of anti-CD20 drugs such as rituximab has been reported to be associated with the appearance of PML in rheumatoid arthritis [10]. However, studies of the prevalence of JCV in patients with neuromyelitis optica (NMO) have not been routinely conducted. These patients may undergo treatment with anti-CD20 monoclonal antibodies.

The risk of developing PML in MS can be stratified, understood, and applied to a population of patients [8]. However, it is essential to establish the prevalence of JCV throughout the entire population in order to make better use of recommendations and guidelines on the risk of PML and PML-IRIS. Although data on the prevalence of JCV in the populations of many countries have been published, no systematic review of these data has been carried out. The proportion of the adult population with antibodies to JCV seems to range from 50.0% to 90.0% [11]. The present paper rigorously reviewed the literature on the prevalence of JCV in patients with MS and NMO throughout the world.

MATERIALS AND METHODS

A rigorous systematic review was carried out using the search terms "JCV" OR "JC virus" AND "multiple sclerosis" OR "MS" OR "NMO" OR "neuromyelitis optica" AND "prevalence." The terms were searched for both in smaller and in larger clusters of words. The databases searched included PubMed, MEDLINE, SciELO, LILACS, Google Scholar, and Embase, and the review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12]. Only papers containing the search words in the title or abstract were included. References listed in papers selected for full consideration were also used to identify any other potentially relevant articles. Only published articles presenting original data on populations of adult subjects with MS were included. Treatment for MS and its potential influence on the results were not considered in the present review. The methods used to assess JCV in human serum were not standardized. Longitudinal studies conducted to assess seroconversion were not considered, and only a single point in time was included, irrespective of treatment duration. Editorials, abstracts, comments, and communications from conferences were excluded. No meta-analysis of the data was carried out; the results were analyzed primarily in a qualitative manner and are presented in tabular format.

Figure 1. The worldwide prevalence (%) of John Cunningham virus according to population-based studies. Detailed information from each country (including the number of patients enrolled) is presented in Table 1.
RESULTS

The initial search returned 1,664 papers, of which 93 were selected by the authors for a full analysis. After discussions, and with all authors’ agreement, 18 articles were included in this review.

In the articles that were analyzed, the presence of JCV in population-based studies was assessed either by means of enzyme-linked immunosorbent assay (ELISA) testing or by second-generation ELISA testing (Focus Diagnostics, Cypress, CA, USA) in serum through [13]. Other methods, such as polymerase chain reaction and urine testing, were only carried out in studies addressing specific patient populations.

The data are summarized in Table 1. Details on the gender, age, and ethnic background of patients were not given in all papers, but there seemed to be an agreement that the prevalence of JCV antibodies increases with age, is higher in men than in women, and is not influenced by ethnicity [14-16]. While some countries only contributed small numbers of subjects, others included thousands. Moreover, while some papers provided information on the prevalence of JCV antibodies in a single country, others reported on several countries and even across continents. The prevalence of positivity for JCV antibodies ranged from 40.0% in Kuwait to 69.5% in Portugal. Interestingly, a second paper from Portugal published 3 years later confirmed this particularly high level of JCV positivity (Table 1). The prevalence of JCV in patients with NMO was assessed in only 1 study, which was conducted in Korea. Positivity for anti-JCV antibodies did not show any continental patterns of distribution, as shown in Table 1 and Figure 1. The systematic review collected data on 29,319 patients with MS/NMO and found that 57.1% of them (16,730 individuals) were seropositive for the anti-JCV antibody.

Although care was taken not to include duplicated data, the present authors cannot be sure that data from the same country in different studies were, indeed, not duplicated. For example, the German population was assessed 4 times and some patients may have been included more than once. Likewise, it is possible that data in the study by Bozic et al. [14] published in 2011 may have been duplicated in later studies [16].

DISCUSSION

The median worldwide prevalence of JCV among adults with MS or NMO was found to be 58.0%. Previous reports mentioned seropositivity rates between 50.0 and 90.0% [11], but the present review showed that it was between 40.0 and 69.0%. This information is important, since therapy planning for demyelinating diseases of the central nervous system relies more and more on monoclonal antibodies that might, ultimately, be associated with the incidence of PML.

Seropositivity for JCV may be subject to a variety of influences and the values reported by different authors may therefore be somewhat skewed. For example, some large studies did not find any association between JCV positivity and the previous use of natalizumab or other immunosuppressive drugs [15,32]. Other authors reported the contrary, finding that seroconversion rates increased by more than 8.0% per year of use of natalizumab [21,28]. A recent meta-analysis of JCV seroconversion during treatment with natalizumab established that the rate of change of serological sta-

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Table 1. Prevalence of JCV antibodies in patients with MS

| Country [Ref] | Year | Total population | With JCV (%) |
|---------------|------|-----------------|-------------|
| Australia [16]| 2014 | 247             | 48.6        |
| Austria [15]  | 2013 | 666             | 66.7        |
| Austria [16]  | 2014 | 192             | 66.7        |
| Belgium [16]  | 2014 | 206             | 66.7        |
| Brazil [17]   | 2013 | 168             | 51.2        |
| Canada [18]   | 2014 | 4,198           | 56.3        |
| Denmark [15]  | 2013 | 1,402           | 52.6        |
| Finland [19]  | 2016 | 503             | 57.4        |
| France [20]   | 2012 | 361             | 51.0        |
| France [15]   | 2013 | 288             | 57.6        |
| France [21]   | 2016 | 1,259           | 59.0        |
| Germany [22]  | 2016 | 2,782           | 58.8        |
| Germany [15]  | 2013 | 3,415           | 59.1        |
| Germany [16]  | 2014 | 1,736           | 61.0        |
| Germany [21]  | 2016 | 1,921           | 54.7        |
| Iran [23]     | 2016 | 85              | 58.6        |
| Ireland [16]  | 2014 | 100             | 51.0        |
| Israel [15]   | 2013 | 495             | 56.6        |
| Italy [15]    | 2013 | 458             | 58.3        |
| Italy [24]    | 2014 | 97              | 53.6        |
| Italy [25]    | 2015 | 37              | 43.2        |
| Korea (NMO) [26]| 2015     | 78              | 69.0        |
| Kuwait [23]   | 2016 | 319             | 44.2        |
| Kuwait [27]   | 2014 | 110             | 40.0        |
| Lebanon [23]  | 2016 | 116             | 55.2        |
| Netherlands [16]| 2014  | 210             | 66.2        |
| Netherlands [28]| 2016  | 179             | 52.0        |
| Norway [15]   | 2013 | 895             | 47.4        |
| Portugal [16] | 2014 | 131             | 69.5        |
| Portugal [29] | 2017 | 371             | 68.2        |
| Saudi Arabia [23]| 2016  | 61              | 45.9        |
| Spain [30]    | 2016 | 711             | 55.3        |
| Spain [31]    | 2017 | 1,061           | 58.2        |
| Sweden [15]   | 2013 | 2,497           | 57.6        |
| Switzerland [16]| 2014 | 54             | 55.6        |
| Turkey [15]   | 2013 | 164             | 67.7        |
| United Kingdom [16]| 2014 | 650             | 48.8        |
| USA [14]      | 2011 | 1,096           | 56.0        |
| **Total**     |      | **29,319**      | **57.1**    |

JCV, John Cunningham virus; MS, multiple sclerosis; NMO, neuromyelitis optica.

*Data published in different countries.*
JCV titers can now be obtained in routine laboratory reports. through second-generation ELISA testing [13], and serum anti-JCV antibodies to JCV in serum has improved the prevalence of anti-JCV antibodies in patients with MS. Likewise, the duration of treatment was 10.8% per year [33]. Therefore, the duration of treatment with natalizumab may be a confounding influence on the prevalence of anti-JCV antibodies in patients with MS. Likewise, the method used for assessing antibodies to JCV in serum has improved through second-generation ELISA testing [13], and serum anti-JCV titers can now be obtained in routine laboratory reports.

For many countries, there are no published data on JCV prevalence. Thus, the present review cannot be considered representative of the whole world. In Central and South America, the only data available are from Brazil. Furthermore, there is no published information on this subject from any country in Africa.

**CONFLICT OF INTEREST**

The authors have no conflicts of interest to declare for this study.

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**REFERENCES**

1. Tan CS, Korcalnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010;9:425-437.
2. Engels EA, Rollison DE, Hartge P, Baris D, Cerhan JR, Severson RK, et al. Antibodies to JC and BK viruses among persons with non-Hodgkin lymphoma. Int J Cancer 2005;117:1013-1019.
3. Tan CS, Ellis LC, Wüthrich C, Ngo L, Broge TA Jr, Saint-Aubyn J, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. J Virol 2010;84:9200-9209.
4. Komagome R, Sawa H, Suzuki T, Suzuki Y, Tanaka S, Atwood WJ, et al. Oligosaccharides as receptors for JC virus. J Virol 2002;76:12992-13000.
5. Fonseca MI, Ni YG, Dunning DD, Miledi R. Distribution of serotonin 2A, 2C and 3 receptor mRNA in spinal cord and medulla oblongata. Brain Res Mol Brain Res 2001;89:11-19.
6. Korcalnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? Ann Neurol 2006;60:162-173.
7. Bauer J, Gold R, Adams O, Lassmann H. Progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome (IRIS). Acta Neuropathol 2015;130:751-764.
8. Mcguigan C, Craner M, Guadagno J, Kapoor R, Mazibrade G, Molyneux P, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry 2016;87:117-125.
9. Misbah SA. Progressive multi-focal leuкоencephalopathy - driven from rarity to clinical mainstream by iatrogenic immunodeficiency. Clin Exp Immunol 2017;188:342-352.
10. Clavel G, Moulignier A, Semerano L. Progressive multifocal leukoencephalopathy and rheumatoid arthritis treatments. Joint Bone Spine 2017;84:671-675.
11. Bellizzi A, Anzivino E, Rodio DM, Palamara AT, Nencioni L, Pietropaolo V. New insights on human polyomavirus JC and pathogenesis of progressive multifocal leukoencephalopathy. Clin Dev Immunol 2013;2013:839719.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-1012.
13. Lee P, Plavina T, Castro A, Berman M, Jaiswal D, Rivas S, et al. A second-generation ELISA (STRATIFY JCV® DxSelect™) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification. J Clin Virol 2013;57:141-146.
14. Bozic C, Richman S, Plavina T, Natarajan A, Scanlon JV, Subramanyam M, et al. Anti-John Cunningham virus antibody prevalence in multiple sclerosis patients: baseline results of STRATIFY-1. Ann Neurol 2011;70:742-750.
15. Olsson T, Achiron A, Alfredsson L, Berger T, Brasat S, Chan A, et al. Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. Mult Scler 2013;19:1533-1538.
16. Bozic C, Subramanyam M, Richman S, Plavina T, Zhang A, Ticho B. Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. Eur J Neurol 2014;21:299-304.
17. Fragoso YD, Mendes MF, Arruda WO, Becker J, Brooks JB, Carvalho Mde J, et al. Nearly one-half of Brazilian patients with multiple sclerosis using natalizumab are DNA-JC virus positive. Arq Neuropsiquiatr 2013;71:780-782.
18. Bhan V, Lapierre Y, Freedman MS, Duquette P, Selch D, Migounov V, et al. Anti-JC virus antibody prevalence in Canadian MS patients. Can J Neurol Sci 2014;41:748-752.
19. Kolasa M, Hагman S, Verkkeniemi-Ahola A, Airas L, Koivisto K, Elovaara I. Anti-JC virus seroprevalence in a Finnish MS cohort. Acta Neurol Scand 2016;133:391-397.
20. Outtercyk O, Ongagna JC, Duhamel A, Zéphir H, Collongues N, Lacour A, et al. Anti-JC virus antibodies in the French cohort of MS patients under natalizumab therapy. J Neuro 2012;259:2293-2298.
21. Schwab N, Schneider-Hohendorn T, Pignolet B, Breuer J, Gross CC, Gobell K, et al. Therapy with natalizumab is associated with high JCV seroconversion and rising JCV index values. Neurol Neuroimmun inflammm 2016;3:e195.
22. Trampé AK, Hemmelmann C, Stroet A, Haghiaka A, Hellwig K, Wiendl H, et al. Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. Neurology 2012;78:1736-1742.
23. Altroughani R, Akhtar S, Ahmed SE, Khoury SJ, Al-Hashel JY, Sahrain MA, et al. JC virus seroprevalence and seroconversion in multiple sclerosis cohort: a Middle-Eastern study. J Neurol Sci 2012;318:134-139.
24. Lanzillo R, Liuzzi R, Vallefuoco L, Moccia M, Amato L, Vacca G, et al. JC virus antibody index in natalizumab-treated patients: correlations with John Cunningham virus DNA and C-reactive protein level. Ther Clin Risk Manag 2014;10:807-814.

25. Delbue S, Elia F, Carloni C, Pecchenini V, Franciotta D, Gastaldi M, et al. JC virus urinary excretion and seroprevalence in natalizumab-treated multiple sclerosis patients. J Neurovirol 2015;21:645-652.

26. Kim SH, Hyun JW, Jeong IH, Joung A, Yeon JL, Dehmel T, et al. Anti-JC virus antibodies in rituximab-treated patients with neuromyelitis optica spectrum disorder. J Neurol 2015;262:696-700.

27. Lamdhade S, Ashkanani A, Alroughani R. Prevalence of Anti-JC virus antibody in multiple sclerosis patients in Kuwait. ISRN Neurol 2014;2014:861091.

28. Vennegoor A, van Rossum JA, Leurs C, Wattjes MP, Rispens T, Murk JL, et al. High cumulative JC virus seroconversion rate during long-term use of natalizumab. Eur J Neurol 2016;23:1079-1085.

29. Correia I, Jesus-Ribeiro J, Batista S, Martins AI, Nunes C, Macário MC, et al. Anti-JCV antibody serostatus and longitudinal evaluation in a Portuguese Multiple Sclerosis population. J Clin Neurosci 2017;45:257-260.

30. Aladro Y, Terrero R, Cerezo M, Ginestal R, Ayuso L, Meca-Lallana V, et al. Anti-JC virus seroprevalence in a Spanish multiple sclerosis cohort: JC virus seroprevalence in Spain. J Neurol Sci 2016;365:16-21.

31. Dominguez-Mozo MI, Rus M, Santiago JL, Izquierdo G, Casanova I, Galan V, et al. Study of the anti-JCV antibody levels in a Spanish multiple sclerosis cohort. Eur J Clin Invest 2017;47:158-166.

32. van Kempen ZLE, Leurs CE, de Vries A, Vennegoor A, Rispens T, Wattjes MP, et al. John Cunningham virus conversion in relation to natalizumab concentration in multiple sclerosis patients. Eur J Neurol 2017;24:1196-1199.

33. Schwab N, Schneider-Hohendorf T, Hoyt T, Gross CC, Meuth SG, Klotz L, et al. Anti-JCV serology during natalizumab treatment: Review and meta-analysis of 17 independent patient cohorts analyzing anti-John Cunningham polyoma virus sero-conversion rates under natalizumab treatment and differences between technical and biological sero-converters. Mult Scler 2017:1352458517728814.