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Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort

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Abstract

JC virus (JCV) is an opportunistic virus known to cause progressive multifocal leukoencephalopathy. Anti-JC virus (Anti-JCV) antibody prevalence in a large, geographically diverse, multi-national multiple sclerosis (MS) cohort was compared in a cross-sectional study. Overall, anti-JCV antibody prevalence was 57.6%. Anti-JCV antibody prevalence in MS patients ranged from approximately 47% to 68% across these countries: Norway, 47.4%; Denmark, 52.6%; Israel, 56.6%; France, 57.6%; Italy, 58.3%; Sweden, 59.0%; Germany, 59.1%; Austria, 66.7% and Turkey, 67.7%. Prevalence increased with age (from 49.5% in patients < 30 years of age to 66.5% in patients ≥ 60 years of age; $p < 0.0001$ comparing all age categories), was lower in females than in males (55.8% versus 61.9%; $p < 0.0001$) and was not affected by prior immunosuppressant or natalizumab use.

Keywords

Multiple sclerosis, JC virus, natalizumab, STRATIFY-JCV, anti-JCV antibodies, epidemiology, infection risk, international study, antibody prevalence, immunosuppressant therapy, brain infection

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Introduction

Progressive multifocal leukoencephalopathy (PML) is an infrequent opportunistic infection of the brain caused by the JC virus (JCV).[1] Evidence of prior JCV exposure, via detectable anti-JCV antibodies, can be used to stratify natalizumab-treated multiple sclerosis (MS) patients at higher or lower risk for PML.[2]

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Table 1. Patient demographics and prior MS treatments.[a]

	Overall (*N* = 10,280)	Austria (*n* = 666)	Denmark (*n* = 1402)	France (*n* = 288)	Germany (*n* = 3415)	Israel (*n* = 495)	Italy (*n* = 458)	Norway (*n* = 895)	Sweden (*n* = 2497)	Turkey (*n* = 164)	*p*-value[b]
Age (years)											
Mean ± SD	39.4 ± 10.5	42.6 ± 12.3	42.5 ± 10.1	36.8 ± 10.1	39.0 ± 9.8	42.1 ± 10.8	35.9 ± 10.2	41.7 ± 10.0	37.5 ± 10.5	32.5 ± 8.7	<0.0001
Median (range)	39.0 (12.0–80.0)	42.1 (17.7–79.8)	42.0 (15.0–80.0)	37.0 (16.0–66.0)	39.2 (16.2–73.5)	40.8 (18.1–78.8)	35.0 (12.0–69.0)	42.0 (12.0–71.0)	37.0 (12.0–75.0)	31.5 (17.0–53.0)	
Sex, female (%)	71.6	71.2	69.8	71.5	73.1	71.3	66.8	69.7	71.9	75.9	0.0767
Disease duration (years)											
Mean ± SD	9.0±6.9	9.0±7.0	11.0±7.2	8.9±7.4	8.2±6.3	11.1±7.7	6.7±5.0	ND	8.3±7.0	7.3±5.0	<0.0001
Median (range)	7.7 (0–48.7)	7.4 (0–41.1)	10.0 (0–47.0)	7.0 (0–42.0)	7.0 (0–48.0)	9.6 (0–43.3)	6.1 (0.4–24.8)	ND	6.6 (0–48.7)	6.4 (0–24.3)	
Immuno-suppressant use (%)[c]	28.0	13.5	10.5	22.8	13.1	70.9	27.4	ND	81.6	15.4	<0.0001
Prior natalizumab use (%)	48.9	8.1	49.4	0	68.5	0	98.0	37.9	45.3	37.7	<0.0001

[a]Estimates in each category (age, sex, disease duration, immunosuppressant use and natalizumab use) were based on information available for that country and the number of patients within that country.
[b]*p*-values comparing all individual countries were obtained using one-way ANOVA for continuous variables and Pearson chi-square test for categorical variables.
[c]The following immunosuppressant agents were used in each country: Austria: azathioprine, cyclophosphamide, methotrexate, mitoxantrone and mycophenolate; Denmark: methylprednisolone and mitoxantrone; France: unknown; Germany: azathioprine, cyclophosphamide, methotrexate and mitoxantrone; Israel: unknown; Italy: azathioprine, mitoxantrone, cyclophosphamide and daclizumab; Norway: unknown; Sweden: methylprednisolone and mitoxantrone; Turkey: azathioprine, cyclophosphamide and mitoxantrone.
ANOVA: analysis of variance; MS: multiple sclerosis; ND: no data available; SD: standard deviation.

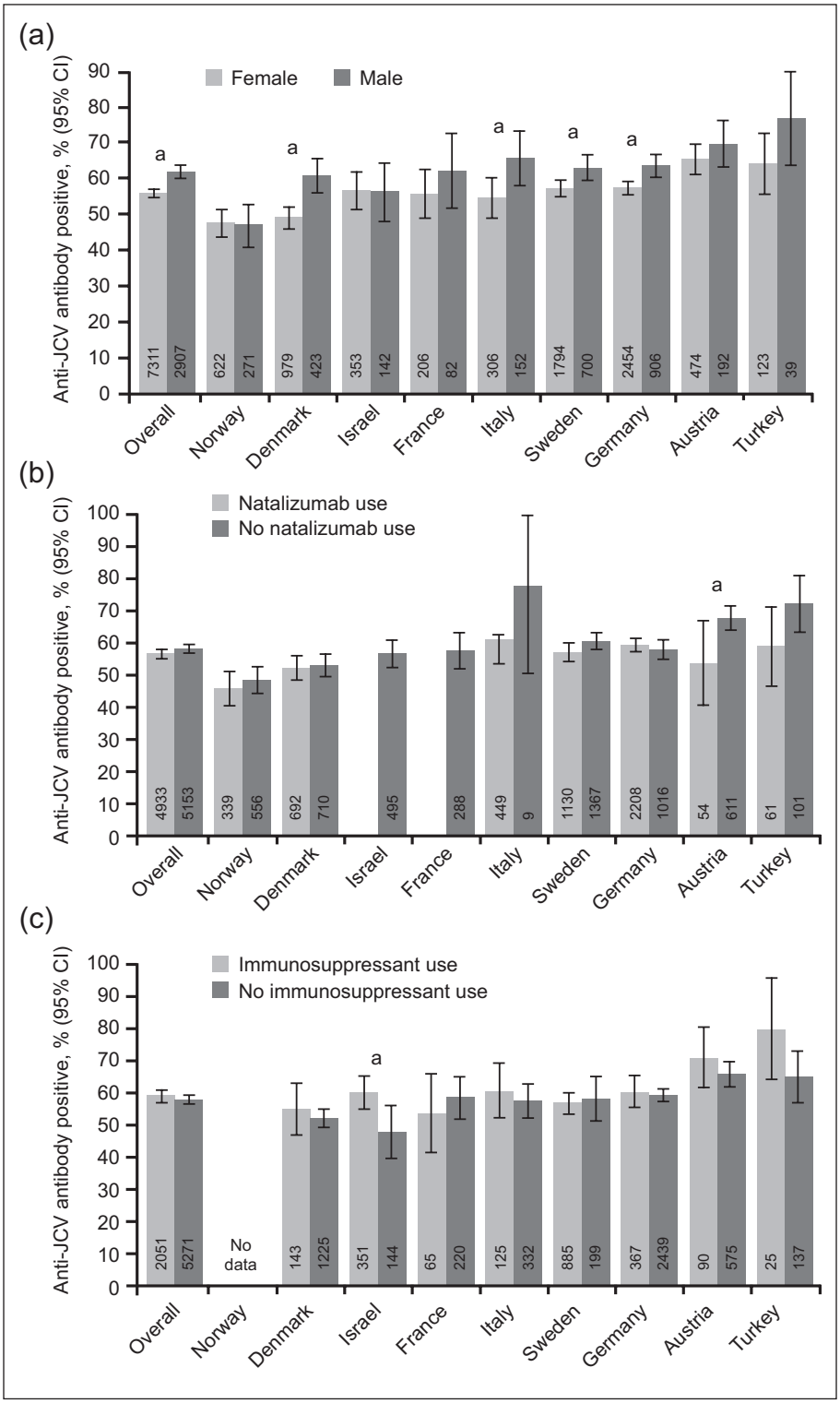

Figure 1. Prevalence of anti-JCV antibodies in (a) female and male patients, (b) patients with and without previous natalizumab use and (c) patients with and without immunosuppressant use overall, and by country. Patient numbers for each group are listed in the columns. There were no natalizumab-treated patients in Israel or France. [a]$p < 0.04$.
JCV: JC virus

It is useful to know the seroprevalence of anti-JCV antibodies in the population of interest and whether seropositivity varies in different geographic areas. We determined the prevalence of anti-JCV antibodies in MS patients in nine countries, and we examined the associations between seropositivity, demographic factors and prior therapies.

Materials and methods

We collected demographic data and either serum or plasma samples from MS patients who were enrolled in approved studies around the world. Information about disease duration and prior immunosuppressant use was not available for Norway. All patients gave written informed consent when required. Samples were stored at −20°C to −80°C until analysis. Data were assembled by the investigators, and stored and analyzed by Biogen Idec and Elan Pharmaceuticals.

The primary endpoint was to define the prevalence of anti-JCV antibodies in each country. Associations between anti-JCV antibody seropositivity and demographic or disease characteristics were evaluated.

STRATIFY JCV™ (Focus Diagnostics, Cypress, CA) is a first-generation assay that was used to detect anti-JCV antibodies.[3] Patient information was blinded during testing.

Summary statistics were used to analyze the anti-JCV antibody prevalence. An analysis of variance (ANOVA) or chi-square test was used to compare the baseline characteristics between countries. We used a chi-square test to assess the bivariate associations between demographic factors and anti-JCV antibody prevalence within individual countries. A logistic regression model, adjusted for age and sex, was used to compare anti-JCV antibody prevalence across countries.

Results

Table 1 shows patient numbers and demographics. The overall prevalence of anti-JCV antibodies in the pooled multinational cohort of 10,280 patients was 57.6% (95% confidence interval (CI), 56.6–58.6). Seroprevalence rates in individual countries were as follows: Norway, 47.4%; Denmark, 52.6%; Israel, 56.6%; France, 57.6%; Italy, 58.3%; Sweden, 59.0%; Germany, 59.1%; Austria, 66.7%; Turkey, 67.7%. The countries with the lowest (Norway and Denmark) and highest (Turkey) seroprevalence had significantly different seroprevalence from most or all other countries (data not shown).

Overall, the prevalence of anti-JCV antibodies tended to increase with age, and it differed significantly across age groups: < 30 years, 49.5%; 30–39 years, 54.8%; 40–49 years, 60.0%; 50–59 years, 67.6%; ≥ 60 years, 66.5% ($p < 0.0001$). In the majority of countries, females had a lower anti-JCV antibody prevalence than males, where the difference was statistically significant within the pooled group, overall (55.8% for females versus 61.9% for males; $p < 0.0001$) and in the Danish, Italian, Swedish and German patient populations (Figure 1(a)).

There was a trend toward lower anti-JCV antibody prevalence in patients exposed to natalizumab (56.7% seropositivity (95% CI, 55.3–58.1%) for exposed patients versus 58.3% seropositivity (95% CI, 56.9–59.6%) for unexposed patients overall; $p = 0.1093$; Figure 1(b)). After adjusting for age and gender, the association between anti-JCV antibody status and previous natalizumab exposure remained nonsignificant ($p = 0.5698$). No Israeli or French patients received natalizumab, and patient numbers were small (< 100) in some of the categories for the other countries, limiting a country-by-country analysis.

Immunosuppressant use data were available for 7324 patients in the pooled multinational cohort; 72.0% (5273 of 7324) did not receive immunosuppressant therapy. The prevalence of anti-JCV antibodies was not affected by immunosuppressant use in the overall population nor in the countries with data available, except in Israel, where anti-JCV seropositivity was more common among patients with prior immunosuppressant use ($p = 0.0129$) (Figure 1(c)). The association between prevalence of anti-JCV antibodies and immunosuppressant use remained nonsignificant, after adjusting for age and gender ($p = 0.7981$).

Discussion

This cross-sectional study found that 57.6% of MS patients in a multinational cohort had detectable anti-JCV antibodies. Except for Norway (47.4%), Austria (66.7%) and Turkey (67.7%), all of the countries had an anti-JCV antibody seroprevalence between 50% and 60%, consistent with other studies using STRATIFY JCV.[3–8] As in previous reports, the prevalence of anti-JCV antibodies increased with age and it was significantly lower in females than in males. [4,6–8] Seropositivity was similar in male and female Israeli patients.[10]

The risk of PML increases with the presence of anti-JCV antibodies, longer duration of natalizumab therapy (particularly > 2 years) and prior immunosuppressant use.[2] We evaluated whether exposure to natalizumab or immunosuppressants had any effect on anti-JCV antibody prevalence. The small (2%) absolute difference in seroprevalence between natalizumab-treated and non-natalizumab-treated patients in this study is unlikely to be clinically significant, particularly because there were no available appropriately-matching samples from both before and after natalizumab treatment.

Overall and in most countries, we found there was no apparent difference in anti-JCV antibody prevalence between patients with and without immunosuppressant use, a result consistent with other studies.[4,6-8] Only in Israel, anti-JCV antibody prevalence was significantly greater in patients with immunosuppressant use than in those without immunosuppressant use; however, the reason for this is unknown.

The limitations of this analysis included the small sample size for some countries (France and Turkey) compared with others (Denmark, Germany and Sweden); the unavailability of prior immunosuppressant information for Norwegian patients; the lack or limited number of natalizumab-treated patients in Israel, France and Austria and of non-natalizumab-treated patients in Italy; and the cross-sectional study design.

The risk of PML is low in patients who are negative for anti-JCV antibodies.[2] In patients across all regions who are receiving or are considering initiating natalizumab therapy, their anti-JCV antibody status should be considered as part of a benefit-risk assessment.

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Conflict of interest

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Thomas Berger has participated in meetings sponsored by and received honoraria (for lectures, advisory boards and consultations) from pharmaceutical companies marketing MS treatments. His institution received financial support through unrestricted research grants (from Allergan, Biogen Idec, Berlex, Bayer, CSL Behring, Merck Serono and Sanofi-aventis) and for participation in randomized controlled trials in MS, sponsored by Bayer Schering, Biogen Idec, Merck Serono, Novartis, Octapharma, Roche, Sanofi, Aventis and Teva.

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Andrew Chan has received personal compensation as a speaker or consultant for Allmirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-aventis and Teva Neuroscience. He has received research support from the German Ministry for Education and Research, Bayer Schering, Biogen Idec, Merck Serono and Novartis.

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Mefkure Eraksoy has received honoraria for advisory boards and lectures/congress support from Biogen/Idec, Bayer HealthCare, Novartis, Merck and Teva.

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Jan Hillert has received honoraria for serving on advisory boards for Biogen Idec and speaker's fees from Biogen Idec, Merck Serono, Bayer-Schering, Teva and Sanofi-aventis. He has served as principal investigator for projects sponsored by, or has received unrestricted research support from, Biogen Idec, Merck Serono, Teva, Novartis and Bayer Schering. His MS research is funded by the Swedish Research Council.

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Authors' note

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