Journal of the Neurological Sciences 360 (2016) 61–65

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

JC virus seroprevalence and seroconversion in multiple sclerosis cohort: A Middle-Eastern study

Raed Alroughani [a,b,*], Saeed Akhtar [c], Samar F. Ahmed [d,e], Samia J. Khoury [f], Jasem Y. Al-Hashel [d,g], Mohammad Ali. Sahraian [h], Mohammed Al Jumah [i,j], Maya Zeineddine [f], Sahar Farhat [k], Hassan Doumiati [k], Bassem I. Yamout [f]

[a] Division of Neurology, Amiri Hospital, Sharq, Kuwait
[b] Neurology clinic, Dasman Diabetes Institute, Dasman, Kuwait
[c] Department of Community Medicine & Behavioural Sciences, Faculty of Medicine, Kuwait University, Jabriya, Kuwait
[d] Department of Neurology, Ibn Sina Hospital, Kuwait City, Kuwait
[e] Department of Neurology and Psychiatry, Minia University, Minia, Egypt
[f] Nehme and Therese Tohme MS Center, American University of Beirut Medical Center, Beirut, Lebanon
[g] Department of Medicine, Faculty of Medicine, Kuwait University, Jabriya, Kuwait
[h] MS Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[i] King Abdullah International Medical Research Center, King Saud Ben Abdulaziz University for Health Sciences, NGHA, Riyadh, Saudi Arabia
[j] Prince Mohammed bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia
[k] Department of Neurology, American University of Beirut Medical Center

ARTICLE INFO

Article history:
Received 5 September 2015
Received in revised form 19 November 2015
Accepted 23 November 2015
Available online 24 November 2015

Keywords:
Multiple sclerosis
Epidemiology
Prevalence
Seroconversion
JC virus
Middle-East

ABSTRACT

Objectives: To estimate JCV seroprevalence and risk of seroconversion against JCV among MS patients in the Middle East.
Methods: This multicenter study was conducted by implementing a cross-sectional design to assess JCV seroprevalence, and a longitudinal design to assess the risk of JCV seroconversion. Multivariable logistic and Poisson regression analyses were used to assess the relationship between clinical variables and JCV seropositivity and risk of seroconversion.
Results: Of 581 MS patients, 64.9% patients were females. Mean age and mean disease duration were 33.9 and 8.4 years respectively. JCV seroprevalence was 48.7%. Male gender ($p = 0.002$), age at onset ($p = 0.001$) and disease duration of 20 or more years ($p = 0.007$) were significantly associated with JCV seropositivity. Among patients (n = 125), followed longitudinally, the risk of JCV seroconversion was 17.6% (95% CI: 11.4%–25.4%) during a median follow-up of 18 months. The proportion of seroreverted and pseudoconverted patients was 4% and 3.2% respectively.
Conclusions: JCV seroprevalence among MS patients in the Middle East was lower than international figures. Male gender, age at onset and disease duration were significantly associated with JCV seropositivity. Risk of JCV seroconversion was higher than previously reported figures. Observed JCV sero-reversion or pseudo-conversion entail watchful period before embarking on a clinical decision.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare, potentially fatal disease of the brain, caused by the John Cunningham Virus (JCV). It is well known that JCV may remain latent for years in uroepithelial tissues, kidneys and, potentially, in other sites such as bone marrow [1]. By means of complex interactions between the host and viral factors, JCV undergoes mutations in the regulatory regions and in the major coat protein. This causes a lytic infection of the brain's oligodendrocytes, which represents the pathogenetic event that drives PML development [2] PML is known to occur in patients with immune deficiency disorders such as AIDS, or prolonged immunosuppressant (IS) use. Its recent association with natalizumab therapy revived interest in this CNS infection [3]. The pathogenesis of PML during NAT treatment is still unclear [4]. The current prevailing hypothesis is that the inhibition of immune cell trafficking into the CNS by natalizumab increases the likelihood of conversion of the archetype to the neurotropic or prototype virus allowing pathogenic forms of JCV to become established which subsequently might prevent adequate immune surveillance in the CNS [5,6]. Recently, a 2-step enzyme-linked immunosorbent assay (ELISA), has been shown to reliably detect anti-JCV antibody in the serum, therefore improving our ability to stratify the

* Corresponding author at: Amiri Hospital, Arabian Gulf Street, Sharq, 13401, Kuwait.
E-mail address: alroughani@gmail.com (R. Alroughani).

http://dx.doi.org/10.1016/j.jns.2015.11.044
0022-510X/

risk of PML in natalizumab treated patients [7]. JCV seropositivity, prior use of immunosuppressants (IS) and natalizumab treatment for more than 2 years are known to be associated with higher risk of PML [8–11]. Reported JCV seroprevalence ranged between 50 and 70% in North America and Europe but these figures were primarily derived from natalizumab-treated patients [12–16]. Initially, the risk of seroconversion against JCV was thought to be 2–3% per year [7,17]. However, a recent study reported an approximately 10% risk of seroconversion against JCV [13]. Given the limited data on JCV seroprevalence in the Middle East, the aims of this study were to determine the JCV seroprevalence, the risk of conversion against JCV and to examine the associated factors among MS patients registered in four regional centers.

2. Patients and methods

This was a multicenter study carried out in four countries of Eastern Mediterranean Region including Kuwait, Lebanon, Iran and Saudi Arabia. We implemented two methodological designs: a cross-sectional study design to assess JCV seroprevalence and evaluate demographic and clinical factors associated with JCV serological status, and a longitudinal study design to determine the risk of seroconversion against JCV. Data from all MS patients who were tested with two-step second-generation ELISA was included [7]. The assays were performed by an independent biological laboratory in Denmark (UNILABS). After the first step, the serum was classified as negative (index <0.20), positive (index >0.40) or indeterminate (index ≥0.20; ≤ 0.40). A second confirmatory step measuring percent inhibition was required for the indeterminate group. The test was considered negative with ≤45% or positive with >45% inhibition. For each patient, data on the country of birth (study center), date of birth, gender, disease course, date of disease onset, disease duration, start and end dates of disease modifying therapies (DMTs), and anti-JCV serostatus including Antibody Index (AI) values were obtained. Based on the literature and biological plausibility, disease duration (years) was divided into 5-year intervals while the number of natalizumab infusions were classified into 5 categories based on 6-month infusion intervals. The initial serological results for the patients were used to compute the JCV seroprevalence (95% confidence interval (CI). For the patients tested negative on first screening, their subsequent repeated serological results were used to assess seroconversion against JCV. Number of seroconverted patients against JCV during follow-up was used to compute the risk (95% CI) of seroconversion against JCV. As stated earlier, the objectives of this evaluation were, i) to estimate JCV seroprevalence and the risk of seroconversion against JCV among patients with MS in the Middle Eastern Region and ii) to examine the association of demographic and disease-specific clinical variables with JCV seropositivity and seroconversion status against JCV using appropriate statistical modeling approach for each of the two outcome variables.

2.1. Statistical analysis

2.1.1. Cross-sectional study

Descriptive statistics including mean (standard deviation [SD]), median (range) or proportion were computed for quantitative and categorical variables as required. As appropriate, chi-square analyses and student's *t* tests were carried out to evaluate the statistical significance of associations of both categorical and quantitative variables with JCV seropositivity. Univariable and multivariable logistic regression analyses were conducted to identify the independent and significant associations of demographic and clinical variables with JCV seropositivity. Adjusted odds ratio (ORs) and their 95% CIs were used to interpret the final multivariable logistic regression model.

2.1.2. Longitudinal study

The risk (number of new converters against JCV/total MS patients JCV seronegative at the beginning of follow-up) of seroconversion against JCV and its 95% CI was computed for patients who were JCV seronegative on first test but seroconverted against JCV in subsequent tests during the follow up period. The statistical significance of relationship of demographic and clinical variables with the risk of seroconversion against JCV was evaluated using Fishers' exact test and quantified using a Poisson regression model with robust variance computation. For all analyses, $p < 0.05$ was considered as significant unless stated otherwise. The local ethical committees in all participating centers approved the study.

3. Results

3.1. Cross-sectional study

A total of 632 patients' records were reviewed. Fifty-one patients were excluded due to incomplete data, and the remaining 581 patients were included in the current study. Of the included cohort, 324 (55.8%) patients performed the initial testing for treatment stratification into natalizumab or other DMTs while 257 (44.2%) performed the initial testing while receiving natalizumab. Women represented 64.9% (n = 377) of the cohort. The mean (±SD) age and disease duration (±SD) were 33.9 ± 9.9 and 8.4 ± 6.5 years respectively. The JCV seroprevalence was 48.7% (283/581) (Table 1). Compared to JCV seronegative patients, JCV seropositive patients were relatively older (mean age = 35.8 ± 9.8 vs.32.1 ± 9.8 years; $p < 0.001$), had higher mean age at disease onset (26.4 ± 9.4 vs. 24.4 ± 8.5 years; $p = 0.008$) and had longer disease duration (years) ($p = 0.001$) (Table 2). However, gender ($p = 0.133$), disease course ($p = 0.948$), prior DMT ($p = 0.214$) and number of natalizumab infusions ($p = 0.223$) did not have statistically significant associations with JCV seropositivity (Table 2). Multivariate logistic regression model showed statistically significant and independent association of male gender (aOR = 2.15; 95% CI: 1.31–3.51), mean age at onset (aOR = 1.05; 95% CI: 1.02–1.08) and disease duration of more than 20 years (aOR = 12.03; 95% CI: 2.96–48.92) with JCV seropositivity (Table 3).

3.2. Longitudinal study

Among 125 JCV seronegative MS patients, who were tested at least twice during the median follow-up period of 18 months (range: 12–

Table 1
Demographic characteristics of the studied cohort (n = 581).

Variable	n (%) or mean ± SD
Country	
Kuwait	319 (54.9)
Saudi Arabia	61 (10.5)
Lebanon	116 (20.0)
Iran	85 (14.6)
Gender	
Female	377 (64.9)
Male	204 (35.1)
Age (years)	33.9 ± 9.9
Age (years) at onset	25.4 ± 9.0
Disease course	
RRMS	524 (90.2)
SPMS	57 (09.8)
Disease duration (years)	8.42 ± 6.50
Prior DMTs use	411 (70.7)
JC virus serostatus	
Negative	298 (51.3)
Positive	283 (48.7)

n: number; SD: standard deviation; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; DMT: disease-modifying therapy.