MSJ Experimental Translational Clinical

Short report

High prevalence and indexes of anti-John Cunningham virus antibodies in a cohort of Chinese patients with multiple sclerosis

Multiple Sclerosis Journal—Experimental, Translational and Clinical

July-September 2018, 1–4

DOI: 10.1177/2055217318788699

Alexander Lau, Wei Qiu, Allan Kermode, Cheryl Au, Angel Ng, Adrian Wong, Sze-Ho Ma, Lisa Au, Karen Ma, Bonaventure Ip and Vincent Mok

Abstract

We performed a cross-sectional study in 123 Chinese multiple sclerosis patients residing in Hong Kong to evaluate their anti-John Cunningham virus status using STRATIFY JCV DxSelect assays. Anti-John Cunningham virus antibody was present in 98/123 (80%) subjects, among which 75/98 (77%) had an anti-John Cunningham virus index $\geq$1.5. Anti-John Cunningham virus antibody seropositivity was not correlated with age, disease duration, Expanded Disability Status Scale scores, types of multiple sclerosis (relapsing vs progressive), or disease-modifying treatments used. We found a very high seroprevalence and index of anti-John Cunningham virus antibodies in Chinese multiple sclerosis patients, which may impact the risk assessment and recommendation of disease-modifying treatments in this population.

Keywords: Anti-John Cunningham virus antibody, Chinese, anti-John Cunningham virus index, progressive multifocal leukoencephalopathy, multiple sclerosis

Date received: 19 May 2018; accepted: 15 June 2018

Background

Despite having a lower disease prevalence, there is an unmet need for Chinese patients with highly active relapsing multiple sclerosis (MS), or patients who have failed to respond to standard treatments.[1] More disease-modifying treatments (DMTs), including fingolimod, natalizumab, and, recently, dimethyl fumarate, teriflunomide, and alemtuzumab, have been introduced to Hong Kong. Nevertheless, the increased risk associated with opportunistic infection of progressive multifocal leukoencephalopathy (PML) and DMT use is a huge concern for health authorities, neurologists, and patients.[2–4] Assessment of antibody status against John Cunningham virus (JCV) is recommended as a risk-stratification tool for natalizumab at drug-initiation and monitoring.[2,5] Yet there is no data on the seroprevalence of anti-JCV antibodies (anti-JCV-Abs) in Chinese patients to help clinicians interpret results and guidelines in practice.[5,6] We performed a cross-sectional study in Chinese patients with MS, aiming to (a) investigate the seroprevalence of anti-JCV-Abs in Chinese MS patients, and (b) identify the associations between clinical characteristics and seropositivity of anti-JCV-Abs.

Methods and subjects

Subjects were recruited from the ongoing prospective Chinese University of Hong Kong Multiple Sclerosis Registry (CU-MSR), which contain local Chinese patients with MS and related central nervous system (CNS) demyelinating diseases. For the current study, we included adult patients aged $\geq$18 years with a diagnosis of MS according to McDonald (2010) criteria; subjects with clinical isolated syndrome and other CNS demyelinating diseases, such as neuromyelitis optica spectrum disorder (NMOSD) or acute disseminated encephalomyelitis (ADEM), were excluded.

Correspondence to:
Alexander Lau,
Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, NT, Hong Kong.
alexlau@cuhk.edu.hk

Alexander Lau, Department of Medicine and Therapeutics, Chinese University of Hong Kong, China

Wei Qiu, Department of Neurology, Third Affiliated Hospital of Sun Yat-sen University, China

Allan Kermode, Perron Institute, University of Western Australia, Australia

Cheryl Au, **Angel Ng**, **Adrian Wong**, **Sze-Ho Ma**, **Lisa Au**,

Karen Ma,
Bonaventure Ip,
Vincent Mok,
Department of Medicine and Therapeutics, Chinese University of Hong Kong, China

[7] The study was approved by the Clinical Research Ethics Committee (CREC-2013.292) and all subjects gave written informed consent.

Laboratory assays

All study samples were shipped from Hong Kong to Unilabs (Copenhagen, Denmark) and stored at a low temperature (<-70°C), until analyzed. Stratify JCV ELISA (STRATIFY JCV DxSelect kit) was used to detect and confirm the presence of anti-JCV-Abs in serum.[5,8] **In** brief, enzyme-linked immunosorbent assay (ELISA) plates were pre-coated with John Cunningham (JC) virus-like particles (VLPs). Samples tested with an index <0.20 were reported as 'seronegative', and an index >0.40 as 'seropositive'. For an index between 0.20–0.40, samples were reported as 'indeterminate', and a confirmatory assay was performed; samples were pre-inhibited with JC VLPs, and the assay was repeated with an uninhibited sample to measure the percentage inhibition; these samples would be reported as 'positive' if inhibition was >45%, or 'negative' if inhibition was ≤45%. The study was performed in compliance with the International Organization for Standardization (ISO) 17025, and in accordance with Good Clinical Practices and Good Clinical Laboratory Practice as appropriate.

Results

Figure 1 shows the patient characteristics in our study. A total of 131 subjects were recruited between 2013–2017. Eight (6%) subjects were excluded in

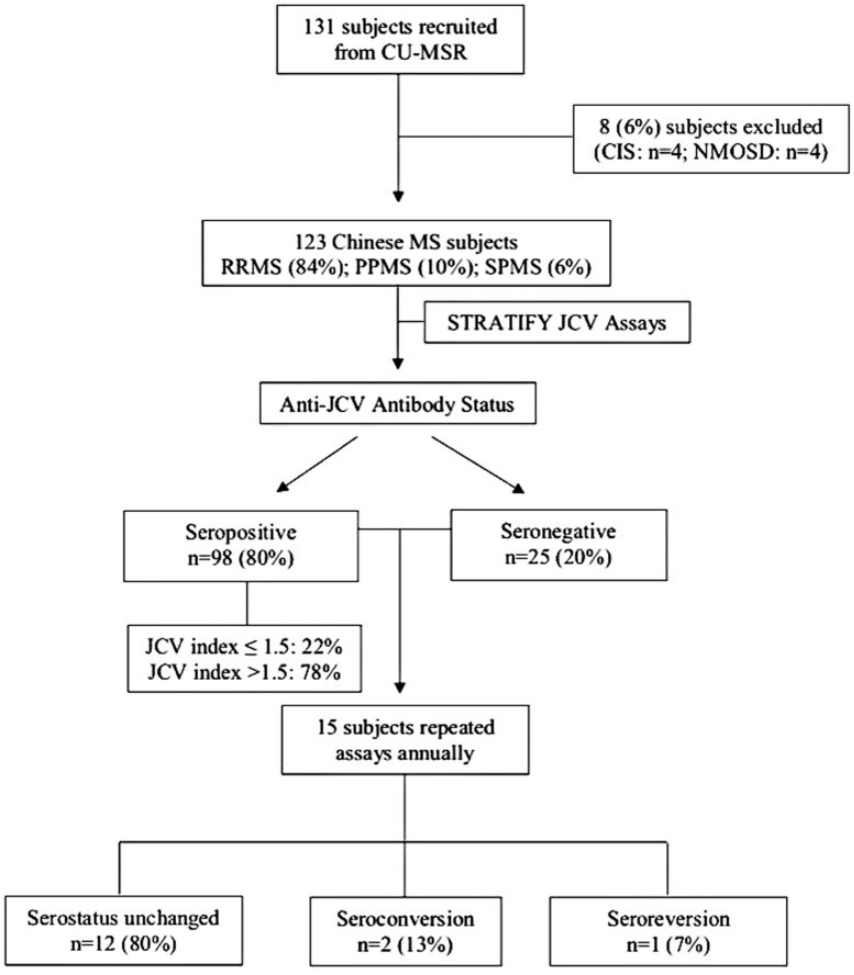

Figure 1. Patient characteristics and serostatus to anti-John Cunningham virus (JCV) antibody assay in a cohort of Chinese patients with multiple sclerosis (MS).
CIS: clinically isolated syndrome; CU-MSR: Chinese University of Hong Kong Multiple Sclerosis Registry; NMOSD: neuromyelitis optica spectrum disorder; PPMS: primary progressive MS; RRMS: relapsing–remitting MS; SPMS: secondary progressive MS.

the analysis for non-MS diagnoses (four clinically isolated syndrome (CIS), four NMOSD). Among 123 subjects analyzed, 15 (12%) subjects underwent repeated testing annually. The MS disease course was relapsing–remitting in 104 (84%), secondary–progressive in seven (6%), and primary–progressive in 12 (10%) subjects. Ninety-six (78%) subjects were female. The median age and disease duration were 36 years (interquartile range (IQR) 28–45) and five years (IQR 2–11), respectively. The median Expanded Disability Status Scale (EDSS) score was 2.0 (IQR 0–5.0). Among relapsing MS subjects, 33 (32%) were treatment-naïve. The ongoing DMTs used were interferon-beta ($n = 56$, 54%), fingolimod ($n = 7$, 7%), and DMF ($n = 1$, 1%).

Overall, 98/123 (80%) subjects were seropositive for anti-JCV-Abs (relapsing–remitting MS (RRMS): 78%, primary progressive MS (PPMS): 83%, secondary progressive MS (SPMS): 100%). The seropositive rates stratified by age quartiles were: ≤20 years: 90%, 21–30 years: 73%, 31–40 years: 86%, 41–50 years: 85%, and >50 years: 81%, respectively. The median anti-JCV index was 3.17 (IQR 0.4–4.1). The distribution of anti-JCV index values was ≤0.60 (7%), 0.61–0.90 (8%), 0.91–1.20 (2%), 1.21–1.50 (4%), and >1.5 (78%), respectively. Subjects with anti-JCV-Abs were of older age (37 vs 32 years), had lower EDSS scores (2.0 vs 3.0), and had shorter disease duration (4.7 vs 5.5 years); but the differences did not reach statistical significance ($p > 0.05$). There was no significant association of anti-JCV-Ab seropositivity with gender (male 74%, female 81%, $p = 0.41$), or types of DMT used (interferon-beta: 73%, fingolimod: 86%, dimethyl fumarate: 100%, $p = 0.32$). In a univariate regression model, age, gender, disease duration, and EDSS score did not predict seropositivity of anti-JCV-Ab.

Among 15 subjects who had repeat testing of anti-JCV-Abs, 12 (80%) subjects remained at the same level of serostatus; two (13%) sero-converted and one (7%) sero-reverted. The anti-JCV index changed from 0.28 to 0.48, and 0.16 to 2.60 in the seroconversion subjects, and 0.29 to 0.23 in the seroreversion subject (reported as indeterminate in the second assay). Four subjects had a third JCV assay and their anti-JCV indexes did not change significantly (0.84, 0.43, 0.76; 2.89, 2.43, 3.06; 3.8, 3.18, 2.94; 3.35, 3.35, 3.95; $p = 0.17$). None of the study subjects developed PML during the study period.

Discussion

We identified a prevalence of anti-JCV-Abs in 80% Chinese MS patients, which is the highest reported rate in the world (47–68%, Figure 2).[9,10] The majority of seropositive MS patients also have a high anti-JCV index (≥1.5), and the sero-status appear to remain unchanged for most subjects in subsequent years. These findings may impact the recommendation of DMT for Chinese MS patients.[6]

The changing paradigm of MS management in recent years has shifted the therapeutic aim from

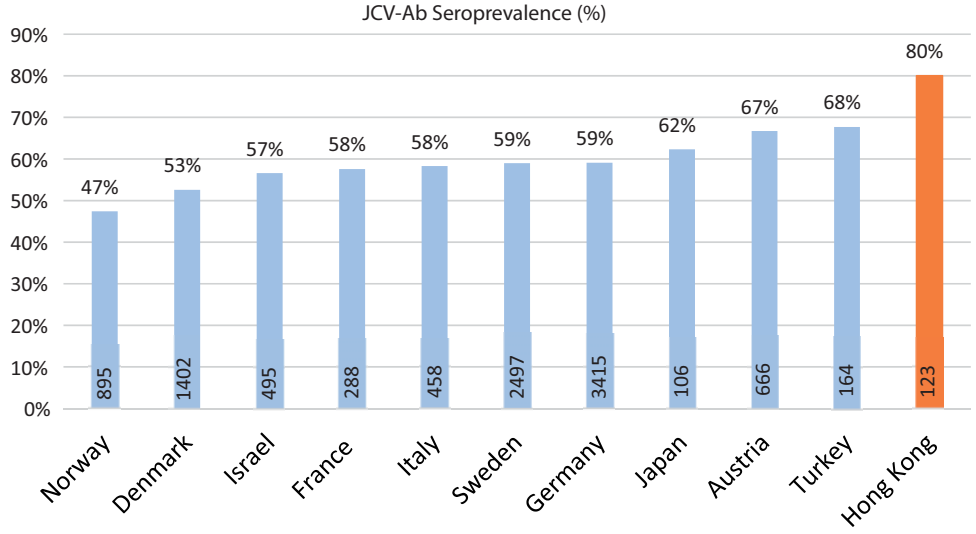

Figure 2. Seroprevalence of anti-John Cunningham virus antibody (JCV-Ab) in multiple sclerosis (MS) patients across different regions in the world.[8,9] Prior exposure to natalizumab was highly variable (0–98%).
*Sample size of studies is shown in the number of individual bars.

reducing relapses and disability to achieving an absence of clinical or magnetic resonance imaging (MRI) activity.[11] Prompt escalation or induction use of potent DMTs is now advocated by neurologists, who are often engaged in discussions on the potentially severe side effects, including PML. Invariably, patients with high anti-JCV index may not want to be exposed to the risk of PML.[9] In other words, patients who have developed highly active disease might consider DMTs with a lower risk of PML, when balancing efficacy and other serious side effects. Further longitudinal studies are required to identify the cause of high prevalence in Chinese people, as a lower seroprevalence (36%) and proportion with high anti-JCV index (≥1.5, 48%) was noted in Perth (personal communication, Communication with Allan Kermode, 17 March 2018), a city of similar latitude and longitude as Hong Kong but in the Southern hemisphere with predominant Anglo-Celtic ethnicity.

Conclusion

The majority of Chinese MS patients in Hong Kong have anti-JCV-Abs and high anti-JCV indexes, which may impact the choice of DMT.

Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Alexander Lau has received research grants, educational grants, and honorarium from Merck, Biogen-Idec, Novartis, Sanofi, and UCB; Allan Kermode has received speaker honoraria and Scientific Advisory Board fees from Bayer, BioCSL, Biogen-Idec, Innate Immunotherapeutics, Lgpharma, Merck, NeuroScientific Biopharmaceuticals, Novartis, Roche, Sanofi-Aventis, Sanofi-Genzyme, and Teva. His department receives grant funding from MS Research Australia, MSWA, the MS Base Foundation, the National Health and Medical Research Council of Australia, and the Trish MS Foundation. He is currently an investigator in pharmaceutical trials sponsored by Biogen-Idec, Novartis, and Merck. All other authors have nothing to disclose.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This investigator-initiated project is funded by Biogen-Idec. The authors had full editorial control over the content of this manuscript.

ORCID iD

Alexander Lau http://orcid.org/0000-0002-5933-9290

References

1. Lau A, Au CCK, Wong A, et al. Clinical features and updated epidemiology data of multiple sclerosis and neuromyelitis optica from the Hong Kong Multiple Sclerosis Registry. *Mult Scler J* 2015; 21: 108–109.
2. Wattjes MP and Warnke C. Guidelines on PML risk stratification and diagnosis in patients with MS treated with natalizumab: So far so good? *J Neurol Neurosurg Psychiatry* 2016; 87: 115.
3. Yoshii F, Moriya Y, Ohnuki T, et al. Neurological safety of fingolimod: An updated review. *Clin Exp Neuroimmunol* 2017; 8: 233–243.
4. Maas RP, Muller-Hansma AH, Esselink RA, et al. Drug-associated progressive multifocal leukoencephalopathy: A clinical, radiological, and cerebrospinal fluid analysis of 326 cases. *J Neurol* 2016; 263: 2004–2021.
5. Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014; 76: 802–812.
6. Ho PR, Koendgen H, Campbell N, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: A retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; 16: 925–933.
7. PolmanC.H., ReingoldS.C., BanwellB., ClanetM., CohenJ.A., FilippiM., FujiharaK., HavrdovaE., HutchinsonM., KapposL., LublinF.D., MontalbanX., O'ConnorP., Sandberg-WollheimM., ThompsonA.J., WaubantE., WeinshenkerB., WolinskyJ.S., Diagnostic criteria for multiple sclerosis: 2010 revisions to the mcdonald criteria, *Ann. Neurol.*. 69(2), 292–302 (2011)
8. Lee P, Plavina T, Castro A, 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.
9. Saida T, Yokoyama K, Sato R, et al. Safety and effectiveness of natalizumab: First report of interim results of post-marketing surveillance in Japan. *Neurol Ther* 2017; 6: 197–211.
10. Olsson T, Achiron A, Alfredsson L, et al. Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. *Mult Scler* 2013; 19: 1533–1538.
11. Comi G, Radaelli M and Soelberg S⊘rensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet* 2017; 389: 1347–1356.