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Multiple sclerosis in First Nations Canadians: A pilot comparison study

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Ruth Ann Marrie, Nicholas Hall and A Dessa Sadovnick

Abstract

Background: Genetic and clinical characteristics associated with multiple sclerosis (MS) may differ by ethnicity but few studies have evaluated whether characteristics of MS differ between individuals according to First Nations (FN) ethnicity.

Objective: Using a cross-sectional observational design, we compared clinical and genetic characteristics between people with MS of FN and non-FN ethnicity.

Methods: We recruited participants of FN ethnicity with MS. We conducted a medical records review for each participant followed by a standardized interview and drawing of blood samples. The blood underwent genetic analyses for several HLA alleles. We compared the study sample with 127 non-FN MS participants from another study conducted in the same region using the same data collection procedures.

Results: We included 144 participants with MS, of whom 17 (11.8%) self-identified as FN. The age of symptom onset was earlier and the diagnostic delay shorter among FN participants although these differences did not reach statistical significance. As compared to non-FN participants, FN participants with MS had increased odds of comorbid psychiatric disease (OR 5.38; 95% CI: 1.84–15.8), and were less likely to be HLA-DRB1*1501 positive (OR 0.32; 95% CI: 0.11–0.96).

Conclusion: Genetic and clinical characteristics of MS differ among Canadians of FN and non-FN ethnicity.

***Keywords*:** Multiple sclerosis, Aboriginal, genetics, epidemiology, psychiatric, HLA

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Introduction

The risk of multiple sclerosis (MS) varies across race and region.[1] Early studies indicated an increased risk of MS in certain racial (Caucasian) and ethnic (Scandinavian and Scottish) groups, and resistance among others including African Americans, Asians and Maori. More recent studies suggest an increasing incidence and prevalence of disease in racial and ethnic groups historically considered at low risk for MS.[2,3] In Alberta, Canada, the prevalence of MS in the First Nations (FN) population increased from 56.3/100,000 in 1994 to 99.9/100,000 in 2002, although it remained lower than in the general population.[2]

Studies in African Americans and Hispanics suggest that race or ethnicity is associated with clinical phenotype, disease severity, treatment response and genetic risk factors in MS.[4–7] However, such differences have not been uniformly observed across populations.[8] An improved understanding of differences between populations may advance our understanding of the etiology of MS and provide insight into the need for population-specific treatment approaches. Little is known about the characteristics of MS in the FN population. A Canadian study suggested that Aboriginal people, including FN, Metis and Inuit populations, with MS had more rapid disability progression than non-Aboriginal people with MS but genetic factors were not evaluated.[9] In 2001, one study of seven FN individuals from Manitoba, Canada with MS noted that five had aggressive disease predominantly involving the optic nerves and spinal cord,[4] consistent with neuromyelitis optica (NMO) rather than MS but current diagnostic criteria[10,11] for these conditions were not applied, challenging the interpretation.

Therefore, we conducted a pilot study to compare clinical and genetic characteristics between people

Correspondence to:
Ruth Ann Marrie
Health Sciences Center, GF-533 820 Sherbrook St, Winnipeg, MB R3A 1R9, Canada
rmarrie@hsc.mb.ca

Ruth Ann Marrie
Department of Internal Medicine, University of Manitoba, Canada
Department of Community Health Sciences, University of Manitoba, Winnipeg, Canada

Nicholas Hall
Department of Internal Medicine, University of Manitoba, Canada

A Dessa Sadovnick
Department of Medical Genetics and Division of Neurology, Faculty of Medicine, University of British Columbia, Canada

with MS of FN and non-FN ethnicity. We also aimed to determine the feasibility of conducting MS research involving FN Canadians given that this requires additional ethical and regulatory steps that vary across provinces.

Materials and methods

We conducted this study in the Canadian province of Manitoba, which has a population of approximately 1.2 million people, of whom more than 140,000 self-identify as FN. Of these, nearly 60% live on reserves (https://www.aadnc-aandc.gc.ca/eng/1100100020400/1100100020404).

Ascertainment

From November 2012 through October 2013, potential study participants were recruited from the MS Clinic in Winnipeg, which serves the entire province of Manitoba. All Manitobans who receive disease-modifying therapy must attend the MS Clinic, irrespective of ethnicity and region of residence. We identified potential participants using the MS Clinic Database, which captures 89% of the clinic population as well as by approaching all people attending routine clinic visits with any provider. We aimed to recruit all individuals with confirmed diagnosis of MS who were of FN ethnicity, defined as having at least one parent of full FN ethnicity. To be an MS case, the participant had to fulfill the McDonald criteria for definite MS.[10,12,13]

Data collection

Data collection included medical records review, a standardized structured telephone interview with the participant, and a blood sample. After obtaining informed consent, a trained research assistant conducted a medical records review to confirm the diagnosis of MS in consultation with a neurologist (RAM) with expertise in MS by verifying the current diagnosis recorded, and the supporting documentation. Clinical characteristics of interest during the records review were age of symptom onset; the diagnostic delay between clinical symptom onset and diagnosis; clinical course, which was classified as relapsing or progressive at onset;[14] and symptoms at onset (optic neuritis, transverse myelitis, non-myelitis related motor, and other). Medical records review was followed by the telephone interview to capture sociodemographics, family history, comorbid diseases and environmental exposures using validated procedures and questionnaires from the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS).[15,16] Comorbidities were categorized as autoimmune, psychiatric, cancer, and other. The psychiatric disorders category captured depression, anxiety disorders, bipolar disorder, and alcoholism. Substance use was not captured. Other conditions included all other health conditions identified in the medical record or reported in the telephone interview such as hypertension. Because of the small sample size, we report only the presence or absence of any comorbidity in a particular category; a participant with more than one psychiatric disorder would simply be coded as affected, the same as a participant with only one psychiatric disorder.

Genetic analysis

Peripheral blood samples were drawn and stored at −20°C. Samples were thawed on ice and 200 microliters of whole blood was used in the DNA purification from blood (spin protocol) from Qiagen. The resulting purified genomic DNA was quantitated by Qubit fluorometric measurement and 130 microliters of DNA was sheared to 600 base pairs with the Covaris S220 focused ultrasonicator. The sheared DNA was visualized on the Agilent Bioanalyzer 2100 using the High-Sensitivity chip and the size was confirmed. Approximately 2 micrograms of sheared genomic DNA was used to create barcoded sequencing libraries using the NEBNext DNA library preparation kit for Illumina. The resulting libraries were then quantitated by Qubit and visualized by Agilent Bioanalyzer 2100 and final library sizes confirmed. Individual libraries were pooled based on quantity and subjected to the custom-designed IDT xGEN lockdown probe four-hour hybridization method for enrichment of the queried human leukocyte antigen (HLA) genes. The final pooled libraries were amplified and quantitated by Qubit, visualized by Bioanalyzer and validated by the KAPA Library Quantitation kit. The libraries were pooled and sequenced on an Illumina MiSeq V2 nano kit with 150 paired end reads (150×2 base pairs)[17] on the MiSeq next-generation sequencer. We amplified all alleles for HLA genes *DRB1*, *DPA1*, *DPB1*, *DQA1*, and *DQB1*. We performed one run using the MiSeq sequencer using eight test samples. As some regions had less than 20 read coverage, the probes used were modified, and the samples re-run at which point coverage of 92%–100% was achieved for each gene. The primary allele of interest for this study was HLA-DRB1*1501. Alleles of secondary interest were those reportedly associated with MS, including DRB1*0301, DRB1*0405, DRB1*0501, DRB1*1602, DQA1*0102, DQB1*0602, DQB1*0402, and HLA-DPB1*0501.[18–21]

Reference database

The Winnipeg MS Clinic enrolled 649 people with MS in the CCPGSMS by approaching all individuals attending clinic visits with any provider from November 2008 to March 2011. Genetic, clinical and family history data on 128 of these participants who had been typed for HLA-DRB1*1501 were used as a comparison group for this pilot study sample because HLA results were available, and ethnicity had been identified previously using the same methods as those used in the present study. One participant within this group of 128 was of FN ethnicity and was removed from the comparison group and used to augment the study sample. Additional typing for other HLA alleles was not available for this group.

Approvals

This study was approved by the University of Manitoba Health Research Ethics Board, and the Health Information Research Governance Committee of the Assembly of Manitoba Chiefs, an organization of FN leaders in Manitoba. We also obtained a research collaboration agreement with the Assembly of Manitoba Chiefs because genetic data were collected, governed by the principles of ownership, control, access and possession (OCAP).[22] The agreement specified that samples would (i) be used only for the stated purpose of this project, (ii) be handled respectfully, (iii) be kept for a limited time, and (iv) be returned or destroyed in a culturally appropriate manner when the agreement ends, and that findings would be shared with the Assembly of Manitoba Chiefs. All participants provided informed consent.

Analysis

As this was a pilot study, we did not conduct formal sample size or power calculations. Categorical variables are reported as frequency (percentage) and continuous variables as mean (standard deviation (SD)). Given the size of the study population, we classified race/ethnicity as FN or non-FN. For genetic analyses we classified individuals having ≥ 1 alleles of interest as positive, and the rest as negative. We evaluated associations between race/ethnicity and categorical variables using chi-square or Fisher's exact tests as appropriate. We evaluated associations between race/ethnicity and continuous variables using Student's *t*-tests or Wilcoxon tests. Again, given that this was a pilot study, we considered it more important to minimize type II error than type I error; the nominal p value was set as <0.05. Statistical analyses were performed using SAS V9.3 (SAS Institute Inc, Cary, NC, USA).

Results

We identified 128 individuals with MS in the CCPGSMS reference database. Of these, one was of FN ethnicity. With respect to new recruitment of FN participants for this study, we identified 43 potential FN participants from the MS clinic database with confirmed diagnoses of MS.[1,12,13] Of these, 12 were eligible based on having at least one parent of full FN ethnicity (others had less FN ethnicity), and agreed to participate. A further four participants who were not in the database were identified by clinic referral. Thus we recruited 16 participants of FN ethnicity. Together with the participant from the reference database we included a total of 17 FN participants with MS in this study. Of the participants who consented, two did not complete structured interviews (one, family illness; one, ongoing psychosocial stressors).

Characteristics of study participants of FN and non-FN ethnicity are summarized in Table 1. Fewer FN participants were female. On average, the age of MS symptom onset was 2.5 years earlier and the diagnostic delay 2.4 years shorter among FN participants than non-FN participants but these differences did not reach statistical significance. Adjusting for sex, neither the age at MS onset ($p = 0.33$) nor the length of the diagnostic delay ($p = 0.12$) differed between the two groups.

There was a tendency for FN participants to present with more motor symptoms at onset ($p = 0.07$), but clinical course at onset did not differ between groups. FN participants had five-fold increased odds of having comorbid psychiatric disease compared to non-FN participants (odds ratio (OR) 5.38; 95% confidence interval (CI): 1.84–15.8), but the frequencies of autoimmune disease and cancer did not differ between groups.

Familial risk of MS was lower among FN than non-FN participants, partly reflecting that individuals from the reference database who had had HLA typing were drawn from multiplex families. The familial risk of 5.9% in first-degree relatives of FN participants is consistent with the expected recurrence risk of 3%–5% in the general Canadian MS population.[18] More than half of non-FN participants with MS were positive for HLA-DRB1*1501. FN participants were less likely to be HLA-DRB1*1501 positive than non-FN participants (OR 0.32; 95% CI: 0.11–0.96).

We evaluated the presence of other HLA alleles only in the FN participants with MS newly recruited for

Table 1. Characteristics of participants with multiple sclerosis according to First Nations status.

Characteristic	Non-First Nations ($n = 127$)	First Nations[a] ($n = 17$)	p value
Female, *n* (%)	96 (75.6)	9 (52.9)	0.048
Age at enrollment (years), mean (SD)	49.6 (10.1)	37.7 (9.2)	0.0001
Age at MS onset (years), mean (SD)	30.7 (9.6)	28.2 (7.9)	0.21
Age at MS diagnosis (years), mean (SD)	35.5 (10.3)	30.8 (8.1)	0.07
Diagnostic delay (years), mean (SD)	5.0 (5.9)	2.6 (3.1)	0.16
Initial symptoms, *n* (%)			
Optic neuritis	26 (27.1)	5 (31.2)	0.77
Transverse myelitis	49 (51.0)	7 (43.7)	0.59
Motor, non-myelitis	17 (17.7)	6 (37.5)	0.07
Other	63 (65.6)	10 (62.5)	0.81
Clinical course at onset, *n* (%)			
Relapsing	91 (96.8)	16 (100)	1.0
Progressive	3 (3.2)	0 (0)	
Comorbid conditions, *n* (%)			
Autoimmune	26 (20.5)	2 (11.8)	0.53
Psychiatric	18 (14.2)	8 (47.1)	0.0009
Cancer	3 (2.4)	0 (0)	1.0
Other	37 (29.1)	11 (64.7)	0.0035
Family history of MS, *n* (%)			
First-degree relatives	58 (45.7)	1 (5.9)	0.0012
Second-degree relatives	15 (11.8)	0 (0)	0.22
Third-degree relatives	40 (31.5)	0 (0)	0.0034
Family history of NMO/NMO-SD, *n* (%)	0 (0)	0 (0)	1.0
HLA-DRB1*1501 (≥1 alleles), *n* (%)	72 (56.7)	5 (29.4)	0.041
HLA-DRB1*0301 (≥1 alleles),[b] *n* (%)	–	0 (0)	
HLA-DRB1*0405 (≥1 alleles),[b] *n* (%)	–	1 (6.7)	
HLA-DRB1*1602 (≥1 alleles),[b] *n* (%)	–	3 (18.7)	
HLA-DPB1*0501 (≥1 alleles),[b] *n* (%)	–	0 (0)	
HLA-DQA1*0102 (≥1 alleles),[b] *n* (%)	–	4 (25.0)	
HLA-DQB1*0402 (≥1 alleles),[b] *n* (%)	–	5 (31.2)	
HLA-DQB1*0602 (≥1 alleles),[b] *n* (%)	–	4 (25.0)	

[a]Sixteen participants newly recruited and one from Canadian Collaborative Project on Genetic Susceptibility to MS. [b]Available only for newly recruited MS participants of First Nations ethnicity ($n = 16$). NMO: neuromyelitis optica; NMO-SD: neuromyelitis optica spectrum disorder; HLA: human leukocyte antigen.

this study ($n = 16$). None of the participants were positive for HLA-DRB*0301 or HLA-DRB*0405, while three (18.7%) were positive for HLA-DRB*1602, four (25.0%) were positive for HLA-DQA*0102, and four (25.0%) were positive for HLA-DQB*0602.

Discussion

This pilot study provided valuable insights into the feasibility of conducting a future national study to more fully explore differences in the genetic and clinical characteristics of people with MS of differing races/ethnicities, specifically those of FN background. The clinical and genetic characteristics of FN and non-FN participants with MS differed.

Although the findings in this pilot study did not reach statistical significance, probably because of the sample size, the age of MS symptom onset was earlier and the diagnostic delay was shorter among FN participants than non-FN participants. In British Columbia, Canada, a cohort of 26 Aboriginal people (mixture of FN, Metis, Inuit) had a similar age of MS onset to non-Aboriginal people with MS, but the diagnostic delay was nearly five years shorter. The authors speculated that possible explanations were

improved awareness of MS in Aboriginal people, and differences in clinical presentation such as more severe attacks. The latter explanation is possible as we observed a tendency toward more motor symptoms at onset in the FN population, and similar findings have been observed in African Americans.[5] We cannot, however, exclude the possibility that selection biases led to the identification of FN participants with more severe disease.

Depression and anxiety are common in the MS population around the world,[23] exceeding the burden in the general population by about two-fold.[24] Depression and anxiety in MS are associated with reduced adherence to disease-modifying therapy, increased cognitive concerns, fatigue, and lower health-related quality of life.[25–27] We found that the burden of psychiatric comorbidity was five-fold greater among FN study participants than non-FN participants. This is consistent with differences observed in the burden of psychiatric comorbidity between FN and non-FN individuals in the general population. In Alberta in 2000, FN people were 2.5 times more likely to seek care for anxiety, and 1.4 times more likely to seek care for depression than non-FN individuals of the same age and sex.[28] Nationally, the frequency of completed suicide and suicide attempts have been reported to be at least two-fold higher in FN populations than in non-FN populations.[29] Further work will be needed to determine whether the combination of FN ethnicity and MS diagnosis confer additive or synergistic risks for psychiatric comorbidity. Several screening tools with adequate sensitivity and sensitivity for depression in MS are available that may assist clinicians in detecting depression;[30] well-validated screening tools for anxiety are more limited.[31]

HLA alleles associated with MS in Northern Europeans include DRB1*1501, DQA1*0102 and DQB1*0602. The frequency of HLA-DRB1*1501 alleles in the MS population differed according to ethnicity, being lower in the FN participants (29.4%) than in non-FN participants (56.7%). Only one other study has reported on the frequency of HLA-DRB1*1501 in FN Canadians with MS and only one of the seven (14.3%) participants had one or more such alleles.[4] However, the study population likely included some people with NMO who were misdiagnosed as MS, given that five participants had disease that principally involved the optic nerves and spinal cord. A prior study conducted in Manitoba and Northwestern Ontario to evaluate the association of HLA with juvenile rheumatoid arthritis in the FN population found that only 2% of controls ($n = 82$) had HLA-DRB1*1501 alleles ($p = 0.0011$ for comparison with our sample).[32] This suggests that although HLA-DRB1*1501 alleles are less common among FN individuals with MS, they are over-represented and confer an increased risk of MS in this population, consistent with many other MS populations.[18] Similarly, we found that the frequency of HLA-DRB1*1602 was more common in our FN sample than in the non-FN rheumatoid arthritis (control) population (18.7% vs. 3%, $p = 0.05$).

Limitations of this study should be considered. Because of the relatively small number of participants recruited, our power to identify differences in clinical characteristics of MS between FN and non-FN participants was limited. However, we expected that MS would be rare in the FN population. We were still able to detect differences in the frequency of the HLA-DRB1*1501 in the FN and non-FN MS populations. The CCPGSMS database included 128 participants with MS who had had HLA-DRB1 testing. They had a higher proportion of positive family histories than the larger CCPGSMS database because of the way in which the sample was selected for HLA testing. However, prior work with the national CCPGSMS database has shown that clinical characteristics of MS did not differ according to genetic load (familial disease risk).[16] We lacked controls to define the underlying frequencies of HLA alleles in the FN population, but a prior study has reported the frequencies of HLA-DRB1 alleles in the Manitoba FN population.[32]

This study highlighted issues relevant to the feasibility of future Canadian studies. Research with the Canadian FN population is governed by the principles of OCAP.[22] That is, FN own, protect and control their information and how it is used. Their communities and bodies control all aspects of research and information management that affect them. FN must have access to data about themselves, and be able to make decisions about access to their information. Possession refers to the physical control of the data. It took a year to obtain a research agreement with the Assembly of Manitoba Chiefs because of concerns regarding the collection of genetic data. The goal of all of these steps was to ensure high-quality, beneficial research carried out in the setting of mutual respect. The specific steps involved in working with FN populations differ from one region to another and must be carefully considered. While the principles of research may be similar, the approaches used to conduct research in indigenous populations in other nations may differ based on cultural concerns and regulations.[33,34]

We were less successful at recruiting people of FN background than anticipated. This may reflect the smaller number of individuals with the desired degree of FN ancestry (at least one parent) in our clinic population than expected based on our preliminary database review. This may also reflect generally lower rates of research participation in this population. In the CCPGSMS, racial/ethnic groups other than Caucasians of north and central European ancestry were less likely to participate (D. Sadovnick, personal communication). In the United States, minority populations have lower rates of participation in research than the white population.[35] Potential barriers to recruitment in minority populations include fear of being used as guinea pigs, the time required to participate, economic constraints, transportation to and from the research location, and lack of real-time benefit to participants.[35] In our study, for example, some potential participants and their family members lived in Northern communities where access to telephones, laboratories and other facilities is more limited than in urban communities. Thus future studies will need to plan for long periods for study initiation, lower recruitment rates, working closely with FN communities to promote the importance of research efforts while respecting individual and community beliefs, and developing ways to support participation of individuals living in remote communities.

Our findings suggest that HLA-DRB1*1501 is associated with susceptibility to MS in FN Canadians. However, the frequency of HLA-DRB1*1501 alleles is lower among FN people with MS than non-FN persons with MS, and our findings implicate other HLA alleles as well. While we did not evaluate differences in environmental exposures, these are also relevant and should be evaluated in the future. Our findings also suggest that attention should be paid to the diagnosis and culturally appropriate management of psychiatric comorbidity in the FN population with MS.

Declaration of conflicting interests

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Nicholas Hall has no conflicts to declare.

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