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AGE AT ONSET OF MULTIPLE SCLEROSIS MAY BE INFLUENCED BY PLACE OF RESIDENCE DURING CHILDHOOD RATHER THAN ANCESTRY.

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CCPGSMS, Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis
HSC, The Hospital for Sick Children
MS, Multiple Sclerosis

ABSTRACT

Multiple Sclerosis (MS) most commonly affects individuals of Northern European descent who live in countries at high latitude. The relative contributions of ancestry, country of birth and residence as determinants of MS risk have been studied in adult MS, but have not been explored in the pediatric MS population. In this study, we compare the demographics of pediatric and adult-onset MS patients cared for in Toronto, Ontario, Canada, a multicultural region. Country of birth, residence during childhood, and ancestry were compared for 44 children and 573 adults. Our results demonstrate that although both the pediatric and adult cohorts were essentially born and raised in the same region of Ontario, Canada, children with MS were more likely to report Caribbean, Asian or Middle Eastern ancestry, and were less likely to have European heritage compared to individuals with adult-onset MS. The difference in ancestry between the pediatric and adult MS cohorts can be explained by two hypotheses:(1) Individuals raised in a region of high MS prevalence, but whose ancestors originate from regions in which MS is rare, have an earlier age of MS onset; or (2) Place of residence during childhood, irrespective of ancestry, determines lifetime MS risk- a fact that will be reflected in a change in the demographics of the adult MS cohort in our region as Canadian-raised children of recent immigrants reach the typical age of adult-onset MS.

INTRODUCTION

Multiple Sclerosis (MS) is the most common cause of neurological disability in young adults and has been most often reported in people of Northern European descent. The prevalence of MS can exceed 200 per 100,000 population in high risk areas such as Scotland, Northern Ireland, and Canada.[1] In contrast, the prevalence of MS in low risk regions, such as Asia, the Middle East and the Caribbean is less than 5 per 100,000 population.[2] It has been suggested that immigration from countries of low MS prevalence to countries where MS is more common results in a heightened individual MS risk, particularly if the person immigrates during childhood.[3] This is illustrated by the increasing frequency of MS in first generation individuals of Asian, African, and West Indian ancestry in the United Kingdom.[4]

Immigration to Toronto, Ontario, Canada (Latitude: 43^{o}, 40' N; Longitude: 79^{o}, 24’ W) has been increasingly represented by individuals from countries of low MS prevalence. The change in immigration patterns, and the presence of well-established pediatric and adult MS programs, provides an opportunity to evaluate the relative contributions of ancestry, country of birth and residence as determinants of MS risk and age of MS onset.

METHODS

Inclusion Criteria: Data were collected on patients with clinically definite MS,[5] ascertained from the pediatric MS clinic at the Hospital for Sick Children (HSC), and the adult MS clinic at St. Michael's Hospital, Toronto, Canada. We included all patients who were residents of Ontario at the time of data collection, as the pediatric and adult MS clinics in Toronto are the major referral centers for persons with MS living in southern and central Ontario. MS clinic patients referred from outside of Ontario were not included. Pediatric MS patients were less than 18 years of age at MS diagnosis

Demographic data acquisition: Clinical and demographic information were obtained by direct patient (and/or parent) interviews and review of medical records. Families were contacted by telephone to complete any missing information. All data from the pediatric MS patients were collected in a systematic manner during clinic visits and entered into the Pediatric Demyelinating Disease database at HSC. The clinic database includes data from patients seen between October 1999 and March 2004. Data for adult MS patients were entered into the Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS) database from August 1993 to January 2003. For inclusion, records from adult MS had to have clear documentation of gender, year of birth, country of birth, residence during childhood, year of MS diagnosis, and ancestry (recorded as one or both of maternal and paternal ancestry). Pediatric and adult MS patients were also classified as Black or non-Black, based on self-classification in the

pediatric cohort and by review of the physician and nursing notes in the chart of the adult patients. Individuals of Asian or Middle Eastern descent were classified as non-Black.

Country of birth: For each patient, specific country of birth was recorded and then grouped according to North America, Europe, the Middle East, Africa, Asia, Oceania, the Caribbean, Central and South America (Table 1).

Residence information: Residence information was recorded and then grouped according to whether or not each participant spent at least 12 months of their childhood (defined as age less than 18 years) in Ontario.

Ancestry: Participants, or parents of participants, were asked to stipulate the country from which their maternal and paternal ancestors originated. Maternal and paternal ancestry was then classified as European, Middle Eastern, African, Asian, Oceanic, Caribbean, Central and South American, or Aboriginal according to the groupings delineated in Table 1. Those patients who identified their ancestors as multi-generational "Canadian" or "American" and not of Aboriginal, African, or Oriental heritage were considered to descendants of the European immigrants that settled in Canada in the last 400 years. Mixed ancestry was defined by having at least one of four grandparents from a different ancestry (as defined in Table 1) as the other three.

Statistical Analyses: Statistical significance between patient groups was established using a commercial software program (PRISM 4®). Binomial data was analyzed using

Fisher’s exact test. The minimum level of significance throughout was $p<0.05$. Data expressed as a percent refers to the proportion of patients for whom this data was available.

RESULTS

Patients: Data on 44 pediatric and 573 adult-onset MS patients meeting the inclusion criteria were available for review. The female to male ratio was 1.32:1 in the pediatric-onset, and 2.5:1 in the adult-onset MS patients. The average age at diagnosis was 12.3 (range: 4.6-17.7) in the pediatric-onset, and 35.2 (range: 18.1-68.6) in the adult-onset MS patients. Fourteen percent of the pediatric and three percent of the adult MS patients were Black.

Country of birth: Country of birth was available for all 44 pediatric and 573 adult MS patients and collated into geographical regions (Table 1, Figure 1). There were more pediatric patients born in Asia ($p=0.0001$) and more adult patients born in Europe ($p=0.0082$). Four hundred and thirty seven (76%) adult-onset, and 35 (82%) of pediatric-onset MS patients were born in Canada. Of the nine pediatric MS patients born outside of Canada, the mean age at immigration was 8.00 years, (range: 3-15 years), and all immigrated prior to age 16 years. One pediatric MS patients was born in Canada, lived in Saudi Arabia from age 1 to 6, and returned to Canada at age 6. For the 136 adult MS patients born outside of Canada, the mean age of immigration was 18.0 years (range: <1 year – 55 years).

Residence during Childhood: As defined by the study inclusion criteria, all pediatric and adult MS patients were residents of Ontario, and patients of the Toronto pediatric and adult MS clinics, at the time of data collection. Thirty-five (81%) of the pediatric MS

patients resided in Ontario from birth, 9 (21%) children immigrated directly to Ontario from countries outside of Canada, as discussed above. Of the 573 adult MS patients, 340 (59%) were born in Ontario and resided in Ontario for their entire childhood, and 24 (4%) were born in Ontario, moved outside of Ontario, and then returned. An additional 88 (15%) patients were not born in Ontario but did reside here during childhood; seven of these 88 patients moved to Ontario in their first year of life. Finally, 121 adults (21%) resided in Ontario as adults, but not during childhood. Overall, 452 (79%) of all adult MS patients included in this study spent some, or most of their childhood in Ontario, which is statistically different than the 100% of the pediatric MS cohort who resided in Ontario for at least a portion of their childhood ($p<0.001$). Of those 121 adult patients who did not reside in Ontario, 37% resided in other regions of Canada during childhood. As stated above, there was no difference in country of birth between the pediatric and adult cohorts.

Ancestry: Maternal and paternal ancestry was available for 43 pediatric MS patients. One pediatric MS patient was adopted. Maternal ancestry was available for 555 adult MS patients and paternal ancestry for 546 adult MS patients. Pediatric MS patients were more likely to report Caribbean (Maternal: $p=0.0177$; Paternal: $p=0.0007$) or Asian (Maternal: $p<0.0001$; Paternal: $p<0.0001$) ancestry compared to adult MS patients. European heritage was significantly more common in adult MS patients (Maternal: $p<0.0001$; Paternal: $p<0.0001$) (Figure 2). Although results did not reach statistical significance, there was a trend for pediatric MS patients to report Middle Eastern ancestry more commonly than the adult MS cohort.

To determine whether ancestry differed among patients with common childhood residence, we compared ancestry of the 43 pediatric and 452 adult patients who spent some or all of their childhood in Ontario. The distribution of ancestry remained essentially the same as that of the entire cohort described above, except that the increased proportion Middle Eastern heritage in the pediatric MS group compared to adult MS reached statistical significance.

DISCUSSION

Pediatric-onset MS patients are more likely to report Caribbean, Asian or Middle Eastern ancestry, and less likely to report European heritage, compared to adult-onset MS patients in the same region. Country of birth did not differ, and 100% of the pediatric and 79% of the adult cohorts spent some or all of their childhood in Ontario, Canada- a region of high MS prevalence. This suggests a prevailing influence of environment on MS risk.

If residence during childhood is the major determinant of MS risk, then the prevalence of MS should be equally distributed among all individuals growing up in the same region, irrespective of their ancestry, and changes in the demographics of the region should be reflected in the demographics of the MS population. In support of this, the pediatric MS clinic population closely reflects the recently changing demographics of our region, as obtained from the 2001 census data [6;7]. Similarly, the adult MS clinic population mirrors data from the 1971 census, obtained when most of the adult MS patients were children growing up in Ontario. At this time, 84% of residents were reported to be of European origin.[8] Given that most adult onset MS patients present between the ages of 25 and 40 years, and assuming that MS risk relates to country of residence during early childhood, the low prevalence of non-Caucasian and non-European patients in the adult MS clinic may simply reflect the previously relatively restricted ethnic diversity of Ontario. If all individuals living in an area of high MS prevalence, such as Ontario,[1] are at near equal risk for MS, then one would expect that the diversity of Ontario-born or

-raised adult MS patients will begin to increase as first generation descendents of Asian, Caribbean, or Middle Eastern immigrants reach the common age of adult-onset MS.

An alternative explanation for the difference in demographics between pediatric and adult-onset MS patients is that, proportionally, individuals of Asian, Caribbean, or Middle Eastern descent develop MS at an earlier age than do individuals of European heritage living in the same region. Many MS patients have evidence of "sub-clinical" demyelinating activity, as evidenced on MRI, that likely predates their clinical presentation by months to years.[9] The length of this sub-clinical period may be influenced by an interaction between environment and ancestry leading to a phenomenon of "precipitated destiny" in which residence during childhood influences not whether the individual develops MS, but rather alters the age at which the individual crosses over the "subclinical" threshold.

There are several recent reviews of the controversies relating to patient grouping by race.[10;11;12] Political and societal perceptions, multiracial heritage, and limited evidence of specific biological determinants of race question the validity of racial classification. The gold standard is that race delineation by done by patient or parental self-report,[10;11] and that authors clearly articulate the need to identify race as a reportable variable. With the above caveats, one particular observation warrants comment. We noted a high percentage (14%) of Black children in the pediatric MS cohort as compared to the adult MS cohort (3%) (Chi square=13.3, df=1, p=0.0003). It has been reported that Black MS patients follow a more aggressive MS course than non-

Black MS patients.[13] Onset of MS during childhood could be considered as a “more aggressive” MS course. Within the pediatric MS cohort, we found that the Black children were diagnosed at a younger average age than the non-Black children (11.1 vs. 12.5 years). Longitudinal assessments are required to determine if Black children experience more frequent relapses or accrue greater disability than do non-Black children.

Evaluation of place of residence during childhood and ancestry in a region in which MS prevalence is high and in which immigration patterns are rapidly changing, has led us to conclude that residence during childhood, rather than ancestry, is a greater demographic determinant of MS risk- at least during childhood. Increased ancestral diversity in the adult MS cohort in our region as Canadian-raised children of recent immigrants reach the typical age of adult-onset MS, would indicate that childhood residence influences lifetime MS risk, not only the onset of MS in childhood. Future studies of the demographic features of the pediatric and adult MS populations in our region over the next 15 years are required to address these issues.

Table 1 Region classification for ancestry and country of birth [14]**.**

Region	**Country**
European[a]	Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Crotia, Czech and Slovak Federal Republic, Denmark, Estonia, Finland, Portugal, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Netherlands, Norway, Poland, Romania, Russia, Spain, Sweden, Switzerland, Ukraine, United Kingdom, Yugoslavia
Middle Eastern	Azerbaijan, Cyprus, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Syria, United Arabic Emirates, Yemen
Asian	Afghanistan, Bangladesh, Burma, Cambodia, China, Hong Kong, India, Indonesia, Iran, Japan, Kampuchea, Korea, Laos, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, Vietnam,
Caribbean	Barbados, Jamaica, St. Vincent, Trinidad and Tobago
Central and South America	Argentina, Bolivia, Brazil, Chile, Columbia, Costa Rica, Ecuador, El salvador, Guatemala, Guyana, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, Venezuela
Africa	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Democratic Republic of the Congo (Kinshasa, formerly Zaire), Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea Bissau, Guinea, Ivory Coast, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Republic of the Congo (Brazzaville), Reunion, Rwanda, Senegal, Seychelles, Sierra Leone, Sao Tome & Principe, Somalia, South Africa, Sudan, Swaziland, Tanzania, Togo, Tunisia, Uganda, Western Sahara, Zambia, Zanzibar, Zimbabwe
Oceania	Australia, New Zealand
Mixed	Ancestry of more than one defined region, i.e. Irish and Jamaican
Aboriginal/ First Nations/Metis (North American)	

[a] Caucasian patients of multi-generational Canadian or American heritage, and not Aboriginal heritage, were classified as European.

Figure 1. Country of birth in pediatric- and adult-onset MS patients. The number of patients is given in parenthesis. * p<0.05; ** p<0.001

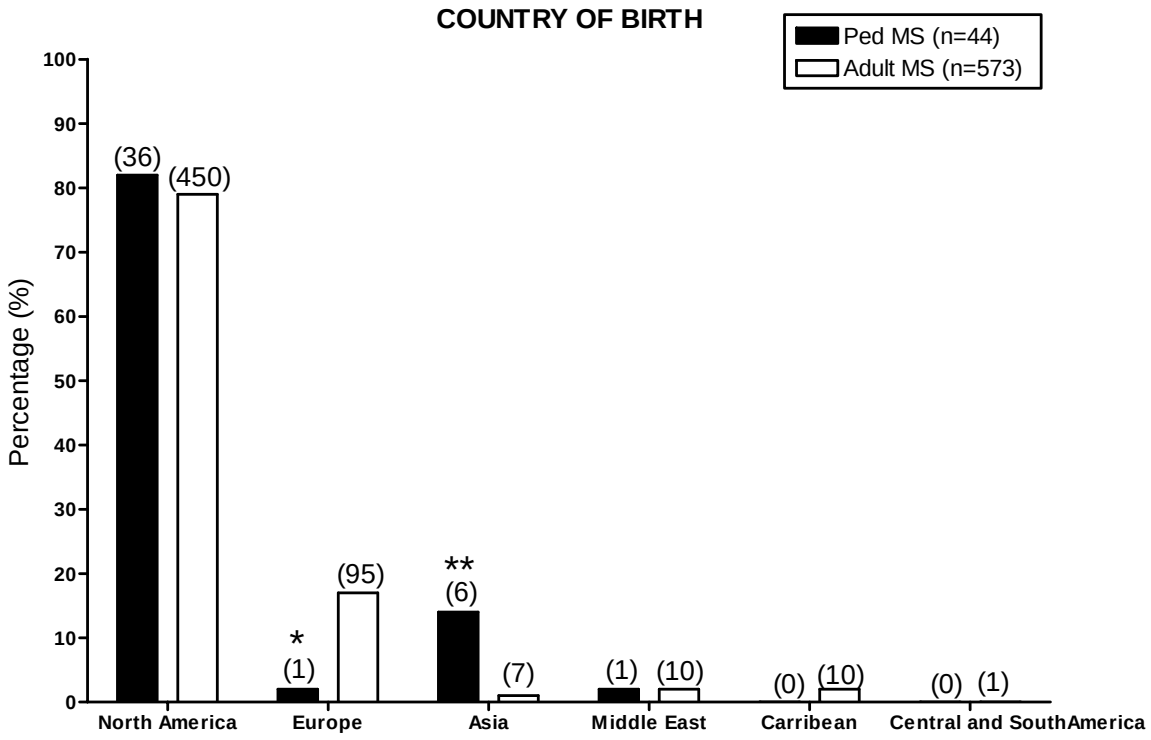
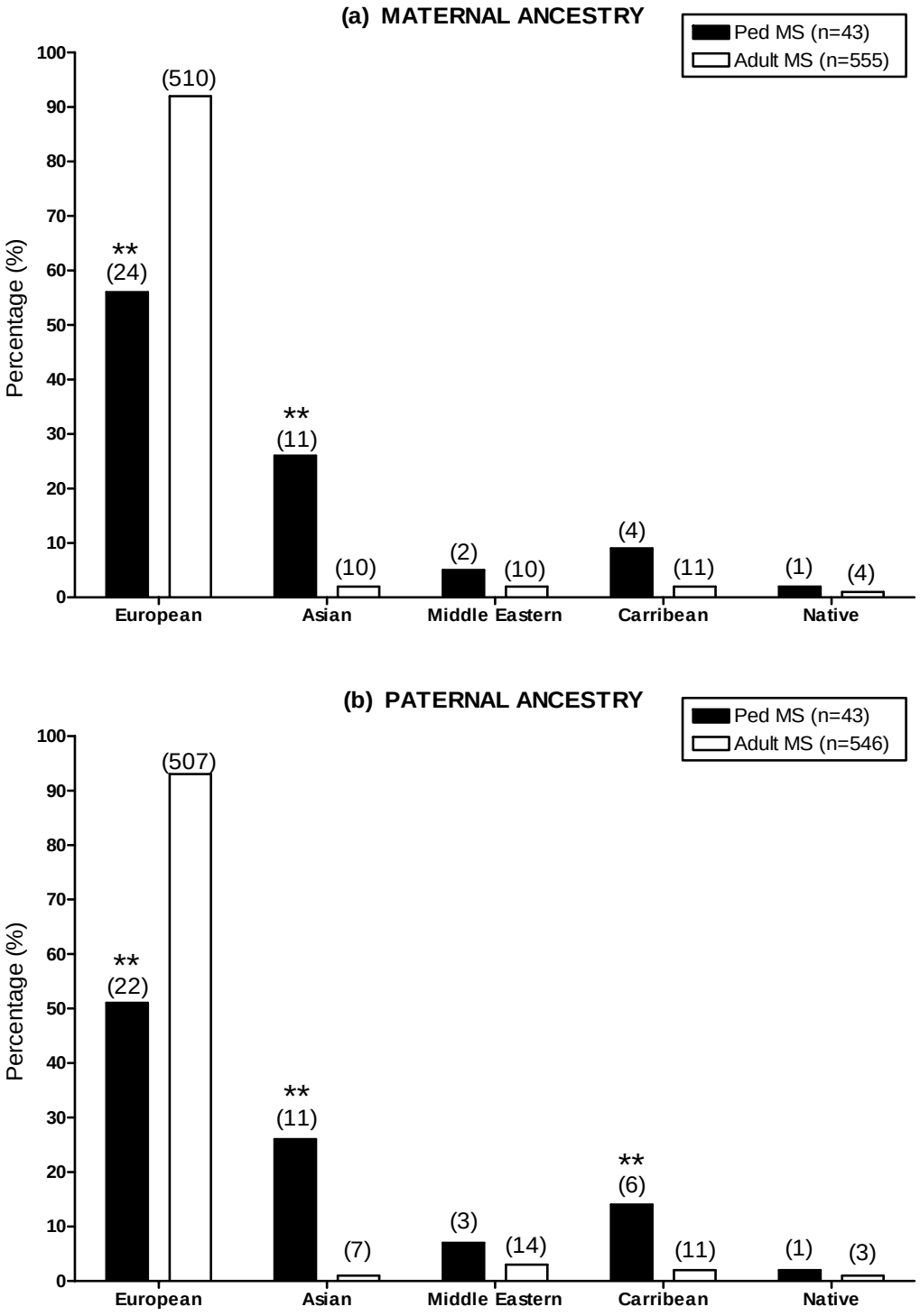


Figure 2. (a) Maternal and (b) paternal ancestry in pediatric-onset and adult-onset MS patients. The number of patients is given in parenthesis. ** p<0.001



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