Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children

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ABSTRACT

Objective: To determine whether the incidence and clinical features of pediatric multiple sclerosis (MS) and other forms of pediatric acquired demyelinating syndromes (ADS) vary by race/ethnicity in a population-based cohort.

Methods: We used a combination of electronic database searches followed by complete medical records review to identify all children diagnosed with MS and ADS in the multiethnic membership of Kaiser Permanente Southern California from January 1, 2004, to December 31, 2009. Incidence rates were standardized to the US census by age and gender.

Results: We identified 81 incident cases of ADS from 4.87 million person-years of observation in children 0–18 years of age. The incidence rate of pediatric MS was 0.51 per 100,000 person-years (95% confidence interval [CI] 0.33–0.75) and incidence of other forms of ADS including optic neuritis, transverse myelitis, other forms of clinically isolated syndrome (CIS), and acute disseminated encephalomyelitis (ADEM) was 1.56 (95% CI 1.23–1.95) for an overall incidence of ADS of 1.66 per 100,000 person-years (95% CI 1.32–2.06). Incidence of ADS was higher in black (4.4 per 100,000 person-years, 95% CI 2.5–7.2, $p < 0.001$) and Asian/Pacific Islander (2.8, 95% CI 1.2–5.2, $p = 0.02$) than white (1.03, 95% CI 0.6–1.7) and Hispanic (1.5, 95% CI 1.1–2.1, per 100,000 person-years) children. Black children were also significantly more likely to have MS than white children ($p = 0.001$). Children who presented with ADEM were significantly younger than children with other types of ADS clinical presentations (mean age 5.6, range 0.7–17.6 years vs 14.6, range 2.7–18.5, respectively).

Conclusions: The incidence of pediatric acquired demyelinating syndromes is 1.66 per 100,000 person-years in a population-based cohort of Southern Californian children. The incidence of ADS and MS is higher in black children compared with white and Hispanic children. *Neurology*® 2011; 77:1143–1148

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **ADS** = acquired demyelinating syndrome; **CI** = confidence interval; **CIS** = clinically isolated syndrome; **KPSC** = Kaiser Permanente Southern California; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **ON** = optic neuritis; **TM** = transverse myelitis.

Multiple sclerosis (MS) is an acquired, chronic inflammatory demyelinating disease of the CNS that is thought to be triggered by environmental factors in genetically susceptible individuals. MS and its potential precursors, optic neuritis (ON), transverse myelitis (TM), clinically isolated syndrome (CIS), and possibly acute disseminated encephalomyelitis (ADEM), collectively known as acquired demyelinating syndrome (ADS), are increasingly recognized in children. Whether this represents increased clinical awareness or increased exposure to environmental triggers during childhood is unclear. Several pediatric MS and ADS cohorts have been established^{1–3} to study this.

The North American pediatric ADS cohorts described broader racial/ethnic diversity than the traditional predominantly Caucasian, adult MS populations. The Northern California cohort² reported a high proportion of Hispanic children (48%) and the Canadian cohort^{1,4}

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Supplemental data at
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Supplemental Data

From the Department of Research and Evaluation (A.L.-G., J.L.Z., J.C., J.Y.) and Neurology Department, Los Angeles Medical Center (A.L.-G., Y.Y.), Kaiser Permanente, Southern California, Los Angeles; and Department of Neurology (A.L.-G., E.W.), University of California, San Francisco.

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reported a high proportion of children of Caribbean, Asian, and Middle Eastern descent. It is unknown whether this increase in racial/ethnic diversity indicates that environmental MS risk factors are becoming more prevalent during childhood among certain minorities or simply reflects a shift in the ethnic distribution of general populations from which these cohorts were obtained.

There is only one previous report of the incidence of pediatric ADS¹ with an overall rate of 0.9 per 100,000 Canadian children. The majority of children in this study were white and pediatric MS and incidence rates stratified by race/ethnicity were not reported.¹ The purpose of this study was to establish estimates of the incidence of pediatric MS and other forms of ADS in a multiethnic population-based cohort of children.

METHODS **Standard protocol approvals, registrations, and patient consents.** The institutional review board at Kaiser Permanente Southern California (KPSC) approved this study. Informed consent was waived as this was a database and chart review study only without direct patient contact.

Case identification. KPSC is a large prepaid health maintenance organization with over 3.2 million members including over 900,000 members 18 years and younger. It provides comprehensive health care coverage to ~20% of the population in the geographic area it serves. The cost of specialist consultations, hospitalizations, MRI scans, other diagnostic tests, and medications is fully covered. The KPSC pediatric membership is representative of the general pediatric population in Southern California with respect to ethnicity, age, gender, and socioeconomic status with the exception of an underrepresentation of the lowest and highest ends of the socioeconomic spectrum.⁵

To identify potentially incident cases, we searched electronic databases for any mention of ICD-9 diagnostic codes for MS and other ADS (see table e-1 on the *Neurology*[®] Web site at www.neurology.org for list of codes) in subjects ≤18 years of age, January 1–December 31 of 2004, 2005, 2006, 2007, 2008, and 2009, including all inpatient and outpatient encounters since enrollment into the health plan (n = 205). Diagnoses were confirmed and additional clinical details were extracted through full medical records abstraction including all inpatient and outpatient records, MRI scans, and diagnostic test results by an MS specialist (A.L.G.) according to the consensus definitions for pediatric ADEM, CIS, neuromyelitis optica (NMO), and MS.⁶ Briefly, ADEM required the presence of encephalopathy in addition to multifocal neurologic deficits. A first CNS demyelinating event without encephalopathy (referable to lesions outside of the optic nerves or spinal cord) was classified as CIS and further subdivided into monofocal or multifocal CIS (deficits referable to a single or multiple CNS lesions, respectively). Pediatric MS was defined as 2 or more episodes of CNS demyelination separated in time and space or a single such episode followed by new gadolinium-enhancing or T2 lesions on MRI scan at least 3 months after the initial event. The presence of ON and TM and

either a spinal MRI lesion extending over 3 or more segments or a NMO-positive antibody was classified as NMO. Complicated cases (n = 11) were adjudicated by a second MS specialist (E.W.) and classified by consensus. All children with optic neuritis had been evaluated by ophthalmologists who confirmed the diagnosis. Idiopathic transverse myelitis was defined according to proposed consensus definitions⁷ after exclusion of infectious, vascular, and other inflammatory causes of myelopathy.⁸

Race and ethnicity. Race and ethnicity information were obtained from medical records review (cases only), health plan administrative records, and birth certificates (all children).⁹ We categorized race and ethnicity as non-Hispanic white, Hispanic white, black (regardless of ethnicity), Asian or Pacific Islander, other or multiple race/ethnicity, and unknown due to missing information. For unknown race and ethnicity information (0% of cases, 45.9% of cohort members), a previously validated imputation algorithm⁵ was used based on birth certificate data (3%), language preference (2.7%), surname (20.9%), and address information geocoded to the US Census Block (11.9%).^{9–12} Those children who remained unknown due to insufficient probability for imputation (7.4%) were assumed to have the same race/ethnicity distribution as the known population. The racial and ethnic distribution of the population remained essentially unaltered after race imputation.

Statistical analyses. Person-years of observation by race/ethnicity were calculated by adding the number of members in each racial/ethnic group at the beginning of the third quarter of each incident year (2004–2009). Confidence intervals for incidence rates assumed that the number of events follow a Poisson distribution. Risk ratios comparing incidence rates between racial/ethnic groups were calculated using χ^2 with Fisher exact test with white non-Hispanic as the reference category. Age was dichotomized based on average age at puberty (0–12, 13–18 years) and gender-adjusted standardized incidence rates were calculated according to the 2000 US Census population. The means and standard deviations of normally distributed variables were compared using 2-sample *t* tests and for binary or categorical variables, χ^2 with Fisher exact test. All analyses were conducted using SAS software v9.1 (Cary, NC).

RESULTS **Incidence.** We identified 81 children newly diagnosed with an ADS between 2004 and 2009. The demographic characteristics of individuals newly diagnosed with ADS are shown in table 1. Children who were initially diagnosed with ON, TM, or other forms of CIS and later developed MS or NMO are included under their initial and subsequent clinical presentations to most accurately represent what we observed in clinical practice. Optic neuritis and other forms of CIS were the most common initial clinical presentations. Of the 19 children who were diagnosed with other forms of CIS, 11 had multifocal signs and symptoms at onset. Most children were diagnosed within 1 month of symptom onset (median 0.3 months, range 0–57.5 months). Most children with MS and other forms of ADS were white Hispanic (49%), consistent with the underlying distribution of the KPSC pediatric patient population during the study period (54.4% white

Table 1 Demographic characteristics of incident pediatric MS and other ADS cases

	MS	ON	TM	Other forms of CIS	NMO	ADEM	Total ADS ^a
Sample size, n	25	29	10	19	3	15	81
Age at first diagnosis, y, mean (range)	15.6 (10.0–18.5)	13.6 (4.0–17.7)	14.4 (7.25–18.0)	13.9 (2.1–17.9)	15.1 (14.4–16.1)	5.6 (0.7–17.6)	12.6 (0.7–18.0)
Female, n (%)	16 (64.0)	17 (58.6)	6 (60)	9 (47.4)	3 (100)	8 (53.3)	46 (56.8)
Race/ethnicity, n (%)							
Hispanic	14 (56.0)	11 (37.9)	6 (60.0)	11 (57.9)	0	8 (53.3)	40 (49.4)
White	2 (8.0)	9 (31.0)	1 (10.0)	2 (10.5)	0	3 (20.0)	15 (18.5)
Black	6 (24.0)	5 (17.2)	2 (20.0)	4 (21.05)	2 (66.7)	3 (20.0)	16 (19.75)
Asian/Pacific Islander	3 (12.0)	4 (13.8)	1 (10.0)	2 (10.5)	1 (33.3)	1 (6.7)	10 (12.35)
Time from symptom onset to diagnosis, mo, median (range)	0.9 (0–25.6)	0.2 (0–6.9)	1.3 (0–47.5)	0.9 (0–7.0)	0.9 (0–23.3)	0.2 (0–5.6)	0.3 (0–57.5)
Duration of KPSC membership prior to diagnosis, y, mean $\pm$ SD	7.6 $\pm$ 6.7	8.6 $\pm$ 5.5	5.3 $\pm$ 5.2	7.0 $\pm$ 6.4	2.0 $\pm$ 2.25	3.2 $\pm$ 2.6	6.6 $\pm$ 5.8
Duration of KPSC membership after diagnosis, y, mean $\pm$ SD	3.3 $\pm$ 1.8	3.3 $\pm$ 2.0	3.2 $\pm$ 1.6	3.5 $\pm$ 2.1	1.6 $\pm$ 0.6	3.0 $\pm$ 1.8	3.3 $\pm$ 1.9

Abbreviations: ADS = acquired demyelinating syndrome; CIS = clinically isolated syndrome; KPSC = Kaiser Permanente Southern California; MS = multiple sclerosis; NMO = neuromyelitis optica; ON = optic neuritis; TM = transverse myelitis.

^a Unique individuals: 3 children had ON then developed MS, 2 had TM then MS; 14 other forms of CIS then MS; and one had TM and then developed NMO.

Hispanic; 29.6% white non-Hispanic; 7.4% black; 7.2% Asian/Pacific Islander; 5.6% other).

The clinical phenotype varied by age with children 12 years and under being more likely to present with ADEM than older children and a lack of a female preponderance among younger children (figure 1).

The incidence of pediatric ADS including MS and other forms of ADS was higher in black and Asian com-

pared with white Hispanic and white non-Hispanic children (figure 2). With white non-Hispanic children as the reference group, the risk of ADS was 4.25 (95% confidence interval [CI] 1.97–9.23; $p < 0.001$) higher in blacks; 2.72 (95% CI 1.09–6.48; $p = 0.02$) in Asians; and 1.45 (95% CI 0.78–2.83; $p = 0.26$) in Hispanic children. The age and gender-adjusted standardized incidence rate and estimated number of US children who are diagnosed with ADS, MS, and other forms of ADS are presented in table 2.

Of the 58 children with incident ON, TM, or other forms of CIS identified during the study period, 20 (34.5%) developed a chronic form of pediatric ADS during the study period after an average follow-up time of 3.25 years (table 1). Nineteen were subsequently diagnosed with MS and one child who presented with TM developed ON within 6 months and was diagnosed with antibody-positive NMO.

In addition to the 19 incident cases of MS and 1 case of NMO described above, we identified 6 more cases of incident MS and 2 more with incident NMO who were diagnosed at initial clinical presentation for a total of 25 incident cases of MS and 3 incident cases of NMO during the study period. Among the 6 additional incident MS cases, 1 patient had been diagnosed with CIS prior to KPSC membership and 5 patients had the initial onset of symptoms while they were KPSC members during the study period; however, their diagnosis of CIS was

Figure 1 Clinical phenotypes of acquired pediatric CNS demyelinating diseases vary with age

This diagram shows the relative distribution of clinical phenotypes in children with acquired demyelinating syndrome 12 years or younger compared with teenagers, 13 to 18 years of age. Acute disseminated encephalomyelitis (ADEM) (in gold) was rare among teenagers ($n = 1$) and multiple sclerosis (MS) (blue) was more common than in younger children. A female preponderance was present among teenagers but not younger children. CIS = clinically isolated syndrome; NMO = neuromyelitis optica; ON = optic neuritis; TM = transverse myelitis.

Figure 2 Incidence of pediatric multiple sclerosis (MS) and acquired demyelinating syndrome (ADS) is higher in black children

This graph shows incidence rates and 95% confidence intervals of pediatric MS (in blue), other forms of ADS (in gold), and all forms of ADS (in green). Black and Asian children have a significantly higher risk of pediatric ADS compared with white and Hispanic children ($p < 0.001$ and $p = 0.02$, respectively). Black children also have a significantly higher risk of pediatric MS compared with whites ($p = 0.001$). The sample size indicates the total number of children with ADS in each group.

missed for the following reasons. In 3 cases the primary care physician and in 1 case the neurologist misdiagnosed the first attack as non-CNS demyelinating diseases and in 1 case the patient did not follow through with neurologic evaluation recommended at the time of initial clinical presentation until after the onset of the second relapse 1.5 years later. The 4 patients who were initially misdiagnosed all developed their second relapse and subsequent diagnosis of MS within 3 to 8 months of their first event. All 5 patients had initial symptoms of monofocal CIS; none presented with ON, TM, or multifocal CIS.

DISCUSSION We found that the incidence of pediatric MS and ADS was very low. In our cohort, black children were unexpectedly found to be at least twice as likely to develop pediatric ADS compared with white children. The incidence of pediatric ADS including pediatric MS was also higher in Asians compared with whites. In contrast, Hispanic children had a similar risk and incidence rate of pediatric ADS and MS compared with whites. While

most of the children with ADS were Hispanic, this reflects the Hispanic predominance of our general pediatric cohort.

Based on our findings, we estimate that the age- and sex-adjusted US census standardized incidence rates for pediatric MS are 0.5 per 100,000 person-years or approximately 380 newly diagnosed cases per year in the United States and 1.63 per 100,000 person-years or approximately 1,250 newly diagnosed children with any acquired demyelinating syndrome per year.

We found a somewhat higher incidence of pediatric ADS than the 0.9 per 100,000 incidence rate previously reported in Canadian children.¹ This modest discrepancy may be because we obtained more complete case capture than the Canadian study, which relied on questionnaires with response rates ranging from 78% to 82%¹ or due to the increased racial and ethnic diversity of our population.

The increase of MS and ADS in black children is a novel finding and suggests that the prevalence of environmental or genetic risk factors may be more common in black compared with white or Hispanic children. It is tempting to speculate that this finding may be explained by the increased prevalence of vitamin D deficiency in dark-skinned individuals.¹³ However, our findings do not clearly follow the skin tone gradient associated with low vitamin D. Thus, it is unlikely that low vitamin D alone could explain why the risk of MS and ADS in Hispanic children is the same as in whites. Future studies should explore other environmental risk factors in addition to vitamin D.

As for candidate genetic factors that could explain our findings, *HLA-DRB1*15* has been consistently as-

Table 2 Standardized incidence rates and estimated number of newly diagnosed children with of pediatric MS and ADS annually in the United States

	MS	Other forms of ADS	All forms of ADS
Standardized incidence rates ^a	0.5 per 100,000	1.5 per 100,000	1.6 per 100,000
Expected newly cases diagnosed annually, n	379	1,171	1,246

Abbreviations: ADS = acquired demyelinating syndrome; MS = multiple sclerosis.

^a Standardized to 2000 US Census; adjusted for age and gender.

sociated with an increased risk of MS^{14–16} but the prevalence of *HLA-DRB1* MS risk allele is lower in blacks than whites¹⁶ and unknown in Hispanics. The possibility remains that either non-HLA MS risk alleles may be more common in black compared with white and Hispanic children or that there is a synergistic interaction between low vitamin D and *HLA-DRB1*15*¹⁷ that is more common in blacks than Hispanics. Future studies of pediatric ADS should include non-MHC risk alleles and stratify analyses by race/ethnicity.

It is unclear whether our findings indicate that environmental or genetic risk factors are different in children compared with adults. There are no published studies comparing incidence rates or prevalence ratios from population-based multiethnic cohorts in either children or adults with MS or other forms of ADS. Blacks are believed to have a lower risk of adult-onset MS than whites but evidence for this comes predominantly from ecological studies and a prevalence study of US veterans published in 1979.¹⁸ Future studies of the incidence of MS in population-based multiethnic cohorts are needed to sort this out.

Consistent with the first pediatric ADS incidence study,¹ we found that pediatric ADS is rare. In fact, the primary limitation of our study is the few incident cases particularly of pediatric MS despite the relatively long observation period. Another limitation of our study is the amount of missing self-reported race/ethnicity information. While we used a validated algorithm based primarily on birth certificates, language preference, and surnames,⁵ our results should be confirmed in future studies with more complete self-reported race/ethnicity information.

Similar to other studies, we found that ADEM is more likely to be a monophasic illness, occurring in young children,^{1,19,20} and that the female preponderance typically seen in adult MS was not present in younger children. In our cohort, none of the children with ADEM developed MS despite similar duration of follow-up with children who presented with ON, TM, and other types of CIS, of whom 34.5% converted to MS. It should be noted that this is one of the first studies reporting the conversion to MS after CIS using the 2007 International Pediatric MS Study Group definitions for ADEM. In the past, ADEM and multifocal CIS were often combined under a first demyelinating attack, which may explain why some authors reported higher conversion rates from ADEM to MS.^{21,22} Thus, our findings suggest that children with ADEM should be examined separately from CIS or MS cases in studies of pediatric MS susceptibility or prognosis as ADEM is often not a precursor to MS.

We found that black children have a higher risk of developing MS and other forms of ADS than white or Hispanic children. This finding is novel and high-

lights that inclusion of minorities in future studies of pediatric and adult MS incidence, susceptibility, and prognosis may reveal important insights into the etiology of MS and other forms of ADS.

AUTHOR CONTRIBUTIONS

Dr. Langer-Gould: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis, study supervision, obtaining funding. J.L. Zhang: analysis or interpretation of data, statistical analysis. J.W.L. Chung: analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Yeung: analysis or interpretation of data, acquisition of data. Dr. Waubant: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. J. Yao: analysis or interpretation of data, acquisition of data, statistical analysis.

DISCLOSURE

Dr. Langer-Gould receives research support from Biogen Idec and her spouse receives research support from the US Veterans Administration and the NIH/NCI. J.L. Zhang, J.W.L. Chung, and Dr. Yeung report no disclosures. Dr. Waubant serves on a data safety monitoring board for the NIH and on a scientific advisory board for Actelion Pharmaceuticals Ltd; has received speaker honoraria from Teva Pharmaceutical Industries Ltd.; served as a consultant for Actelion Pharmaceuticals Ltd, Roche, and sanofi-aventis; and receives research support from sanofi-aventis, Biogen Idec, the NIH, the National MS Society, and the Nancy Davis Foundation. J. Yao reports no disclosures.

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