

Relative Incidence of Inherited White Matter Disorders in Childhood to Acquired Pediatric Demyelinating Disorders

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Epidemiologic frequencies of pediatric white matter disorders as a class have not been well defined. This is particularly true of genetic disorders of the white matter of the brain. In this study, ICD-9 codes were used to estimate relative incidence rates and descriptive statistics of leukodystrophies, other genetic leukoencephalopathies and acquired demyelinating disease among children residing in the Washington, D.C. metropolitan area. Children being treated at US children's hospitals between January 1, 2004, and December 31, 2009, for acquired demyelinating disease or genetic white matter disorders were captured using the Pediatric Health Information System and the Physician Practice Management system and validated with local electronic medical records. Comparisons were made between genetic white matter disorders and acquired demyelinating disorders, to determine differences in incidence, age, gender, ethnicity, and mortality. Genetic causes of white matter disease identified with ICD-9 codes had an estimated incidence of 1.2/100,000 children in the Washington, DC area. What was of interest was nearly 5 out of 10 cases of pediatric white matter disease of any etiology were attributable to genetic causes. When only progressive white matter diseases were considered, 7 out of 10 cases were attributable to genetic causes, and only 3 out of 10 to progressive acquired demyelinating disease such as multiple sclerosis. These findings signify the important contribution of heritable white matter disorders to pediatric neurologic disease in the Washington, DC, metro area as well as throughout the United States. Continued research of these understudied disorders should compare disease incidence and determinants to validate these findings in different populations.

Semin Pediatr Neurol 19:219-223 Published by Elsevier Inc.

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Adeline Vanderver, MD, is supported by grants from NINDS, the Dana Foundation and the Seventh Framework Program.

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Limited information exists about the incidence of genetic white matter disorders of the brain. Genetic white matter disorders of the brain include classic leukodystrophies as well as other heritable disorders with prominent white matter abnormalities shown on neuroimaging, referred to here as genetic leukoencephalopathies. Previous studies using national health reporting systems in Germany estimated incidence of heritable white matter disorders to be approximately 1 in 50,000 live births.¹ However, more recent studies conducted using statewide data in Utah estimated incidence of any heritable white matter disorder as 1 per 8000 live births.³ The wide discrepancy between these estimates is surprising, even taking into account differences in populations and classification of patients as having a leukodystrophy. Further research to establish incidence outside these 2 distinct populations^{1,3} and additional descriptive statistics such as mean age at diagnosis and mortality in patients with leukodystrophy^{2,3} are needed to establish relevance to public health.

In contrast, awareness of acquired demyelinating disorders is greater than that of leukodystrophies, which are individually perceived to be rare entities and not as common as the acquired demyelinating disorders, even in the pediatric population. In this study, acquired white matter disorders include multiple sclerosis (MS), transverse myelitis (TM), optic neuritis (ON), acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO). It is estimated that 2.7%-5% of patients with MS are below 16 years of age.^{4,5} In Canada, incidence of acquired white matter disorders was estimated to be 0.9/100,000 children.⁶ A recent publication of acquired white matter disorders in southern California identified an incidence of 1.66/100,000 children⁷ and similar data was obtained in the Netherlands with an incidence of 0.66/100,000 children.⁸ We hypothesize that despite commonly held perceptions, children are at least as commonly affected by inherited disorders of the white matter of the brain as by acquired demyelinating disorders. In this study we present relative incidence data of acquired demyelinating disease and genetic disorder of the white matter in the pediatric population.

Methods

A retrospective cohort study design was used and approved by the Children's National Medical Center (CNMC) Institutional Review Board. CNMC is a 284 bed acute care pediatric academic medical center with more than 40 subspecialties in a major metropolitan area. ICD-9 codes most likely to capture white matter disorders were identified (Table 1). Data on only patients between the ages of 0-18 years were collected. Databases used included the Pediatric Health Information System (PHIS) (ambulatory surgery, Emergency Room and inpatient visits), the Physician Practice Management (PPM) system (outpatient visits), and the CNMC Myelin Disorders clinic patient records.

PHIS were used to capture patients seen at CNMC in ambulatory surgery, the Emergency Room and inpatient visits at CNMC. PHIS is an administrative database that contains inpatient data from 40 not-for-profit, tertiary care pediatric hospitals across the United States. Data quality and reliability are assured through a joint effort between the Child Health Corporation of America (Shawnee Mission, KS), and participating hospitals. Discharge data are de-identified at the time of data submission and subjected to a number of reliability and validity checks before being processed into data quality reports. The PPM system and the CNMC Myelin Disorders clinic patient records were used to identify outpatient visits also at CNMC. All children diagnosed with white matter disorders (genetic or acquired) from January 1, 2004, to December 31, 2009, at CNMC were collected. Retrospective chart review was performed on patients with qualifying ICD-9 codes using an electronic medical record (EMR) system (PowerChart). Duplicate cases were excluded.

Variables collected from confirmed cases using the EMR included state of residence, zip code, date of birth, gender, race or ethnicity, age at initial medical visit for white matter disease, length of time to diagnose and the final diagnosis. Mortality for CNMC cases was determined using information in the EMR or by physician confirmation. Patients with degenerative disorders who had not returned to CNMC for follow-up for more than 3 years and where no knowledge of death was available, were excluded from mortality statistics. The length of time for diagnosis was determined as the difference between the first visit for white matter disease and the date of either a confirmed diagnosis or confirmation that the patient has an unclassified disorder, once extensive clinical testing pertinent to the disease presentation had failed to reveal a known disorder. Race and ethnicity were assigned consistent with the definition of the 2000 Census of Population Public Law 94-171, US Census Bureau. To protect human subjects, all data was de-

Table 1 ICD-9 Codes Used to Identify CNMC Cases in the PPM and PHIS Databases

Heritable White Matter Disorders		Acquired White Matter Disorders	
ICD-9 Code	Description	ICD-9 Code	Description
330.00	Leukodystrophy	341.20	Acute 'transverse' myelitis
330.10	Cerebral lipidoses	341.21	Acute 'transverse' myelitis in conditions classified elsewhere
330.20	Cerebral degeneration in generalized lipidoses	341.22	Idiopathic TM
330.30	Cerebral degeneration of childhood in other diseases classified elsewhere	323.82	Other cases of myelitis
330.80	Other specified cerebral degenerations in childhood	340.00	MS
330.90	Unspecified cerebral degeneration in childhood	341.00	Neuromyelitis optica
349.89	Other specified disorders of nervous system	377.30	Optic neuritis
323.90	Unspecified cause of encephalitis, myelitis, and encephalomyelitis)	377.32	Retro bulbar neuritis 'acute'
341.90	Demyelinating disease of central nervous system, unspecified	323.61	Infectious acute disseminated encephalomyelitis 'ADEM'
		323.63	Post infectious myelitis
		323.81	Other causes of encephalitis and encephalomyelitis

Table 2 List of Specific Disorders Included as Leukodystrophy and Genetic Leukoencephalopathy Within the CNMC Dataset

A. Leukodystrophy	Number of Cases	B. Genetic Leukoencephalopathy	Number of Cases
Adrenoleukodystrophy	3	Aicardi Goutières syndrome	4
Alexander Disease	6	Congenital disorder of glycosylation	1
CACH/Vanishing white matter disease	1	Fucosidosis	1
Canavan disease	1	GM1/GM2	5
Hypomyelination-unsolved	5	Interstitial deletion of 18q chromosome	1
Krabbe	1	Mitochondrial (MELAS, Kearns Sayre, pyruvate dehydrogenase deficiency, POLG1)	6
Megalencephalic leukodystrophy with subcortical cysts	1	MTHFR deficiency	2
Metachromatic leukodystrophy	5	Mucopolysaccharidoses	3
Pelizaeus Merzbacher disease	6	Neuronal Ceroid Lipofuscinosis	2
Pelizaeus Merzbacher like disease (GJC2)	1	Salla disease	1
Unsolved leukodystrophy	20	Peroxisomal biogenesis disorder and Neonatal Adrenoleukodystrophy	2
Total	50		28

identified prior to analysis; only the above variables were extracted and examined by investigators.

Disorders were classified either as acquired demyelinating disorders, leukodystrophies or heritable leukoencephalopathies. Acquired demyelinating disorders included MS, NMO, TM, ON and ADEM. Classification of patients with heritable disorders identified in our CNMC population as leukodystrophies and determined by the authors was established (Table 2). Certain disorders not considered classic leukodystrophies but significantly affecting white matter were included as genetic leukoencephalopathies if they were heritable and had prominent white matter abnormalities (Table 2).

Statistical Analysis Software version 9.1 was used to conduct all analyses. Cases were classified as one of 3 groups: acquired white matter disorders, leukodystrophies, or genetic leukoencephalopathies. For CNMC cases, frequency distributions were determined for all variables, and a one-way analysis of variance (ANOVA) procedure was used to determine whether differences in time to diagnosis and age at diagnosis existed between the 3 groups. Tukey's studentized range test allowed for multiple comparisons within the model. Lastly, incidence within the Washington, D.C. metropolitan area among children of ages 0 through 19 years for each white matter disorder group was calculated using population data estimated in CDC's Wonder surveillance system. Patients were grouped according to the year of birth and the year of presentation and compared on a same year basis to average birth rates within those time periods.

Results

A data query of ICD-9 codes from the PPM and PHIS databases generated 704 possible cases of white matter disease; 455 patients did not meet the inclusion criteria for white matter disorders because other disease states, including malignancy, infection, and vascular disease, were

identified (Supplementary Data, Table 1), 68 were duplicates and 16 were non-metropolitan cases. The 165 remaining patients included 50 leukodystrophy cases (Table 2A), 28 genetic leukoencephalopathy cases (Table 2B), and 87 acquired white matter disorder cases. In our leukodystrophy group, 20 out of 50 cases had not achieved a specific etiologic diagnosis (40%), which was comparable to previous estimates of unsolved cases in large groups of patients affected by leukodystrophies⁹. Males made up the majority of each group, but females made up a larger proportion in the acquired group as compared to the inherited group (35% vs 17%) (Supplementary Data, Table 2). Frequency distributions indicate approximately half of all cases resided in Maryland (Supplemental Data, Table 3). Nearly twice as many cases of acquired white matter disorders were black than white (26% vs 11.5%) (Supplementary Data, Table 4). An estimated 15 deaths occurred, all seen in the genetic white matter disorder cases (22% mortality vs 0%) (Supplementary Data, Table 2).

Incidence rates were calculated to include all children considered 'at risk' for white matter disease between January 1, 2004 through December 31, 2009 using population estimates of children up to the age of 19 and residing in counties considered within the Washington, DC metropolitan area (Table 3). The incidence of leukodystrophy was 7.56 cases per million children and Incidence of genetic leukoencephalopathy was 4.23 cases per million children in the Washington, DC metropolitan population, with a cumulative incidence for genetic white matter disease of 11.79 cases per million children. Incidence of acquired white matter disorders was 13.14 cases per million children. A fourth comparison group, progressive acquired white matter disorders, was created to compare incidence rates only and included those patients with NMO, MS, and other cases of acquired demyelinating disease with progressive symptoms. This incidence of progressive acquired white matter disorders was 4.83 cases per million children. Incidence of either a heritable or acquired white matter disorder was 24.93 cases per million

Table 3 Incidence of White Matter Disorder Groups Among Children

Disorder	PHIS and PPM CNMC Dataset*
MS	27 cases (4.08 cases/1 million children) [†]
Neuromyelitis optica	5 cases (0.76 cases/1 million children)
TM	5 cases (0.76 cases/1 million children)
ON	19 cases (2.87 cases/1 million cases)
Acute disseminated encephalomyelitis	26 cases (3.93 cases/1 million children)
Leukodystrophy	50 cases (7.56 cases/1 million children)
Genetic leukoencephalopathy	28 cases (4.23 cases/1 million children)
Total progressive acquired white matter [‡]	32 cases (4.83 cases/1 million children)
Total acquired white matter	87 cases (13.14 cases/1 million children)
Total inherited white matter	78 cases (11.79 cases/1 million children)
Total acquired and inherited white matter disease	165 (24.9 cases/1 million)

PHIS, Pediatric Health Information System; PPM, Physician Practice Management system; CNMC, Children's National Medical Center.

All cases 0-19 years diagnosed with white matter disorders between January 1, 2004 to December 31, 2009

*CDC Wonder Surveillance Census projection estimates for the years 2004-2009 for children aged 0-19: 6, 619, 841 children in the DC metro area (denominator used to calculate incidence estimates).

†An additional 5 cases of progressive acquired white matter not otherwise specified (NOS) were identified that did not fulfill full criteria for MS but are still reflected in the total progressive acquired white matter disorder cases.

‡Total progressive acquired demyelinating disorders included MS, and NMO.

children. Proportion of total children with white matter disease having leukodystrophy or genetic leukoencephalopathy was $47.27\% \pm 10.01\%$; 99% Confidence Interval. Proportion of total children with a progressive white matter disorder having leukodystrophy or genetic leukoencephalopathy was $70.19\% \pm 11.16\%$; 99% Confidence Interval.

Among CNMC data, the mean time from original presentation to diagnosis was 1 year and 4 months in the leukodystrophy group, 9 months in other genetic leukoencephalopathies, and 5 months in the acquired demyelinating group ($P < 0.01$; Supplementary Data, Table 2). The acquired white matter group had a mean age at diagnosis of 10 years, significantly higher than for the genetic leukodystrophies ($P < 0.0001$). Mean age at diagnosis for leukodystrophies (6 years) and genetic leukoencephalopathies (4 years) showed no significant difference (Supplementary Data, Table 2).

Discussion

In the Washington, DC metropolitan region, confirmed cases of genetic pediatric white matter disease were more than twice as common as progressive acquired white matter disease (MS and NMO) and nearly as common as all forms of acquired white matter disease combined. The incidence in the Washington, DC region (approximately 1.2 per 100,000 children) for genetic white matter disease is relatively close to previous incidence rates of 1/100,000 described for these disorders as a group,¹ though considerably less than some recent studies which suggested the incidence might be as high as 1/8000.³ This discrepancy may represent differences in patient capture or in case definition. Additionally, other disease specific studies of incidence, such as in adrenoleukodystrophy, are often based on biochemical and DNA sequencing test results, and as such ascertain cases very differently than our study which was based on symptomatic patients seeking

treatment.¹⁰ Population demographics may also contribute to this difference. Within a racially and ethnically diverse population in the Washington, DC metropolitan area, 33% of leukodystrophy cases were African American, 58% were Caucasian and 13% Hispanic. This suggests that these disorders also clearly affect a broad range of ethnic and racial populations.

In this population, we also validated previous findings of an incidence of pediatric acquired demyelinating disease of approximately 1-1.5/100,000.^{6,7} For the purposes of this study, it is assumed that a significant proportion of children with acquired and inherited disorders of white matter living in the Washington, DC, metropolitan area would be referred to this institution. It is also assumed that the proportion of children with acquired or genetic white matter disorders referred to CNMC would be similar to that of the general population. The fact that our incidence values of acquired demyelinating disease are similar to those established in other studies suggests that we have adequately captured cases in this geographic area.^{6,7}

An additional limitation of this study design was the difficulty of using ICD-9 codes in epidemiologic studies. This may be particularly true for inherited white matter disorders of the brain for which very few have specific ICD-9 codes, contrary to acquired white matter disorders. Therefore, our incidence values may under represent the true incidence of heritable white matter disorders of the brain due to the difficulty of detecting subjects with rare disorders using only ICD-9 data.

Although this study was done at an institution where a specialized clinic attracts patients with acquired and genetic white matter disease, care was taken to exclude all cases from outside a defined geographic area. The denominator used comprised population estimates from CDC's Wonder surveillance system, which is considered a leading source of population information and should be a relatively accurate population number. Overall, these limitations are not likely to provide a bias towards either

acquired or genetic cases of white matter disease but rather demonstrate the critical need for future research to provide better incidence estimates of these disorders throughout the US. Incidence rates in our studies were similar to those done in some previous studies

Additional findings of interest in the Washington, DC, population include statistically significant differences in mortality, which may reflect the fact that acquired disorders are more often monophasic. Leukodystrophies were also notable for a statistically significant increase in time to diagnosis from first presentation, which may be due to the difficulties of achieving a specific diagnosis in this population or due to the inherent acute nature of presentations of ON, TM, ADEM or even MS. Our study population was consistent with the current literature in that nearly 50% of the leukodystrophy patients had a heritable white matter disorder of unknown origin.⁹ The combination of increased incidence and mortality, and prolonged time to diagnosis suggests that there may be a significant health impact, both emotionally and financially, for children with a leukodystrophy and their families and communities.

Finally, certain acquired white matter diseases present as monophasic events and may result in full recovery. Conversely, inherited white matter disorders of the brain are degenerative disorders with deteriorating neurologic function over time.¹¹ We hypothesize that the burden of disease is significant in children and families with leukodystrophies or genetic leukoencephalopathies. This is because of the significant morbidity of these disorders, the difficulty in achieving a diagnosis and their incidence. Together, the frequency and morbidity of heritable white matter disorders justifies further study as well as increased awareness.

Conclusions

The incidence of pediatric heritable disorders of the white matter (approximately 1/100,000 children) is at least equal to that of progressive acquired demyelinating disorders such as MS and NMO, and possibly as great as all acquired demyelinating disorders combined in the pediatric age

group, including MS, NMO, ADEM, TM, and ON. In addition, increased mortality, uncertainty and length of time of diagnosis in genetic white matter disease compounds the effect of these devastating disorders. Further study is necessary to establish a more precise estimate for the incidence of heritable white matter disease overall and of specific leukodystrophies.

Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.spen.2012.10.001>.

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