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Acquisition of Early Developmental Milestones and Need for Special Education Services in Pediatric Multiple Sclerosis

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GA contributed to the design of the study, acquisition and analysis of the data, wrote the first draft and provided subsequent edits of the manuscript. MW contributed to the design of the study, analysis of the data, and critically revised the manuscript. WV, NM, EW and LK contributed to the design of the study, acquisition and analysis of the data, and critically revised the manuscript. JN, YH, TC, LB, MC, TC, MG, JG, BG, TL, SM, JMT, MR, MR, JR, JR, TS, AW, BWG and AB contributed to the acquisition and analysis of the data and critically revised the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved at each site's institutional review board

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Abstract

Children with pediatric-onset multiple sclerosis and pediatric controls were enrolled across 16 pediatric multiple sclerosis centers in the United States and completed questionnaires that addressed time of first unaided walking and acquisition of two-word phrases. A total of 467 (308 female) cases and 428 (209 female) controls were enrolled. Pediatric multiple sclerosis (n=467) were not delayed in walking or using two-word phrases compared to healthy controls (n=428) (2.2% vs 5.7% respectively). Children with disease onset before age 11 vs. onset at 11 years or after were more likely to need an individualized education plan (p=0.002), reading assistance (p=0.0003) and math assistance (p=0.001). Children with multiple sclerosis onset prior to age 18 are not delayed in meeting the two major early developmental milestones but do have a significantly increased use of special services or learning assistance at school. Further research will need to address whether other measures of development (e.g rate of language acquisition or fine motor skills) differ between pediatric multiple sclerosis and controls.

Keywords

pediatric; multiple sclerosis; developmental milestones; cognitive impairment

Introduction

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system that typically affects young adults but can also develop in children and adolescents.[1–3] Patients with pediatric-onset multiple sclerosis have more frequent exacerbations and more T2-bright lesions on brain magnetic resonance imaging scans at onset as compared to adults.[4]

Cognitive impairment after multiple sclerosis diagnosis occurs[5] in about one-third of pediatric patients[6–8] and one-half or more of adults with multiple sclerosis. Impairment depends in part on disease duration.[9] Children with clinically isolated syndrome also have cognitive deficits detectable shortly after disease onset.[7] The course of cognitive impairment in children has varied across studies. In an Italian cohort of 63 patients in whom 48 were retested over 5 years, more than half worsened.[10] However, in an United States cohort[11] tested twice over 1.6 years as well as in a Canadian group tested twice over 1 year,[12] there was little change in mean scores. What was most notable was that far fewer of those with pediatric multiple sclerosis improved (18%) on repeated testing compared to healthy controls in whom 86% improved, suggesting a failure to acquire age appropriate skills.

Children with chronic diseases such as diabetes, epilepsy and spina bifida have impaired school performance.[13–15] Previous studies have assessed performance by absenteeism and academic testing. Low socioeconomic status and parental education level were the major predictors for poor school performance. In children with acquired demyelinating syndromes, the French "KIDSEP" study group utilized grade retention as a marker for academic performance.[16] The cohort was monitored for an average of eight years, during which 44% of patients repeated a grade. Risk factors for grade retention included being male, low socioeconomic status, and being older than 11 years at disease onset.

Acquisition of early motor and verbal developmental milestones in healthy children includes being able to walk independently by 12–15 months and using two-word phrases by 24 months.[17] Not meeting developmental milestones on time is correlated with poor intelligence later in life.[18]

It is remarkable that in childhood-onset multiple sclerosis, cognitive changes can be detected early after disease onset while residual physical symptoms from first demyelinating events tend to recover very well or completely.[19,20] Our a priori hypothesis was that there is cognitive dysfunction and impairment of early milestone acquisition before first detected clinical multiple sclerosis event.

Methods

This study was conducted as part of a larger case-control study investigating environmental and genetic risk factors for pediatric multiple sclerosis conducted at 16 multiple sclerosis centers, most of which participate in the United States Network of Pediatric Multiple Sclerosis Centers. Parents or legal guardians of cases and controls completed a questionnaire (http://www.usnpmsc.org/Documents/EnvironmentalAssessment.pdf) asking whether the child walked independently by 15 months of age and used two-word phrases by 24 months of age. Parents could respond in one of two ways: they could report the exact age in months or select from a range (less than 12 months, between 12–15 months, more than 15 months and unknown). Responses of "unknown" were treated as missing in the analysis. As part of an ongoing registry study in pediatric multiple sclerosis, families of multiple sclerosis subjects also completed a separate questionnaire that captured information on need for special education services. These data were not captured in the healthy control group as controls were not enrolled in the registry. Data from all questionnaires were merged into a single database.

Cases included children with relapsing-remitting multiple sclerosis or first demyelinating event and at least two silent magnetic resonance imaging lesions, with disease onset prior to 18 years of age. Diagnosis was ascertained by a panel of at least two pediatric multiple sclerosis experts for all cases enrolled in the case-control study. Age matched controls were recruited in the general and subspecialty clinics at participating institutions with the majority recruited from general pediatric clinics. Controls were not recruited from neurology clinics nor were they related to multiple sclerosis subjects and did not have other neurological disease. Inclusion criteria for controls were absence of any autoimmune disease, except asthma and eczema and no parent with multiple sclerosis. Institutional Review Board

approval was obtained at all participating sites and written informed consent obtained from parents and assent from subjects as required. The Data Coordinating and Analysis Center at the University of Utah maintained and analyzed data.

All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). We described the cases and controls using frequencies and percentages for the categorical variables and means, standard deviations, and ranges for continuous variables. Logistic regression models, adjusting for sex, were used to determine the effect of case/control status on developmental milestones.

We compared use of special services between those with very early disease onset (age < 11) and those with later disease onset (age ≥ 11) using Fisher's exact test. Eleven years was used as a cut-off as has been used in prior pediatric multiple sclerosis studies.[3,16,21] Multivariable logistic regression models were used to determine an association of special services with early disease onset adjusting for disease duration, gender, race/ethnicity, and mother's education.

Results

A total of 467 cases (308; 67% female) with mean age at first event of 13.5 years (median 14.7, SD 3.8) and 428 controls (209; 49% female) were enrolled (see table 1). Mean age at enrollment was 15.4 years for cases and 14 years for controls. The mean disease duration at time of enrollment was 11.5 months (median 8.5, SD 12). The mean age at first event was 7.1 years (median 7.2, SD 2.7) in those with multiple sclerosis onset prior to age 11, and 15.1 years (median 15.4, minimum 11.1, maximum 19.2; SD 1.8) in those with onset at or after age 11.

As compared to healthy controls, children with multiple sclerosis were less likely to have walked after 15 months compared to controls (2.2% vs 5.7%, p=0.01). There was no difference in using two-word phrases after 24 months between multiple sclerosis subjects and healthy controls (2.4% vs 5.2%, p=0.07). In multivariable models adjusting for sex, cases were significantly less likely to walk at more than 15 months than controls (OR=0.37, 95% CI=0.16, 0.82, p=0.01). There were no statistically significant differences between cases and controls for using the first two-word phrase when adjusting for sex. We were unable to adjust for race and mother's education due to small cell sizes.

Subjects with first symptoms prior to age 11 were more likely to require an individualized education plan, occupational therapy, reading assistance and math assistance compared to subjects with multiple sclerosis onset at age 11 or older (see table 2). Children received special services prior to multiple sclerosis diagnosis in 9.2% of patients with diagnosis prior to age 11 versus 10.5% with diagnosis after age 11 (p=0.84).

In multivariable analysis, adjusting for disease duration, sex, race/ethnicity, and mother's education, those having disease onset prior to age 11 had four times the odds to receive occupational therapy (95% CI=1.43,11.89, p=0.01). They were also more likely to receive assistance in reading (OR 2.73, 95% CI=1.12, 6.65, p=0.03) and math (OR 3.13, 95% CI=1.36–7.22, p=0.01) (see table 3).

Discussion

We observed that children who develop pediatric multiple sclerosis are not delayed, relative to healthy controls, in acquisition of early motor and verbal developmental milestones of walking independently and using two-word phrases. In adults there is evidence of a disease prodrome prior to the first demyelinating event.[22] In fact, our data show that pediatric multiple sclerosis patients were less likely to be delayed in walking independently than healthy controls. Our results suggest that in patients with multiple sclerosis diagnosed in childhood the disease prodrome may not extend into the infancy and toddler period. It is possible that inflammation does extend this far but that time to walking independently and using two words phrases are not sensitive enough measures to detect subtle changes in toddlers. These data are in contrast with reports that some patients who go on to develop multiple sclerosis-like demyelination have genetic predispositions to abnormal white matter development.[23]

When comparing children with very early onset multiple sclerosis (age < 11) to later-onset multiple sclerosis, the younger group required an individualized education program, occupational therapy, and assistance in reading and math more frequently, possibly reflecting a longer duration of inflammatory brain activity and/or greater vulnerability of the developing brain. Adjusting for disease duration, race/ethnicity and mother's education, children with very early onset multiple sclerosis were more likely to receive occupational therapy, reading assistance as well as math assistance. The greater need for special education activities in very early onset multiple sclerosis is in line with previous reports of more significant cognitive impairment in children with pre-pubertal onset multiple sclerosis[24]but are in contrast to the KIDSEP cohort where onset of an acquired demyelinating syndrome after age 11 was associated with a greater risk of grade retention.[16] Early initiation of disease modifying treatment may slow cognitive impairment in adults.[25–27] Future studies are needed to determine the cost-effectiveness of early initiation of disease modifying treatment in children in improving academic performance and thereby reducing the need for special education services.

Strengths of our study include the large and diverse cohort of well-characterized multiple sclerosis subjects and adjustments for possible confounders. A significant limitation is the self-report nature of milestones that occurred on average over a decade prior to study enrollment. Previous studies that have examined contemporary recording of milestone attainment with parental recall several years later have shown that reliability decreases over time.[28] However, we would expect recall accuracy of parents of cases and controls to be similar. Other limitations include the restricted capture of milestone data on the questionnaire, the lack of precise timing on initiation of individualized education program and other services relative to the date of multiple sclerosis diagnosis.

Future research should investigate evidence of very early cognitive impairment utilizing extended and more sensitive developmental metrics as well as whether use of special education services improve developmental outcomes.

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References

1. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Multiple sclerosis. 2009;15(5):627–631. [PubMed: 19299440]
2. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Multiple sclerosis. 2013;19(10):1261–1267. [PubMed: 23572237]
3. Belman AL, Krupp LB, Olsen CS, et al. Characteristics of Children and Adolescents With Multiple Sclerosis. Pediatrics. 2016;138(1).
4. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. INcreased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Archives of neurology. 2009;66(1):54–59. [PubMed: 19139299]
5. Banwell BL, Anderson PE. The cognitive burden of multiple sclerosis in children. Neurology. 2005;64(5):891–894. [PubMed: 15753431]
6. Amato MP, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. Neurology. 2008;70(20):1891–1897. [PubMed: 18474844]
7. Julian L, Serafin D, Charvet L, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. Journal of child neurology. 2013;28(1):102–107. [PubMed: 23155206]
8. Till C, Ghassemi R, Aubert-Broche B, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. Neuropsychology. 2011;25(3):319–332. [PubMed: 21534686]
9. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. Neurology. 1991;41(5):685–691. [PubMed: 2027484]
10. Amato MP, Goretti B, Ghezzi A, et al. Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. Neurology. 2014;83(16):1432–1438. [PubMed: 25217060]
11. Charvet LE, O'Donnell EH, Belman AL, et al. Longitudinal evaluation of cognitive functioning in pediatric multiple sclerosis: report from the US Pediatric Multiple Sclerosis Network. Multiple sclerosis. 2014;20(11):1502–1510. [PubMed: 24687807]
12. Till C, Racine N, Araujo D, et al. Changes in cognitive performance over a 1-year period in children and adolescents with multiple sclerosis. Neuropsychology. 2013;27(2):210–219. [PubMed: 23527649]
13. Fowler MG, Johnson MP, Atkinson SS. School achievement and absence in children with chronic health conditions. The Journal of pediatrics. 1985;106(4):683–687. [PubMed: 3981326]
14. Dahlquist G, Kallen B, Swedish Childhood Diabetes Study G. School performance in children with type 1 diabetes--a population-based register study. Diabetologia. 2007;50(5):957–964. [PubMed: 17333107]
15. Taras H, Potts-Datema W. Chronic health conditions and student performance at school. J Sch Health. 2005;75(7):255–266. [PubMed: 16102088]
16. Mikaeloff Y, Caridade G, Billard C, Bouyer J, Tardieu M. School performance in a cohort of children with CNS inflammatory demyelination. European Journal of Paediatric Neurology. 2010;14(5):418–424. [PubMed: 20207560]
17. Scharf RJ, Scharf GJ, Stroustrup A. Developmental Milestones. Pediatrics in Review. 2016;37(1):25–38. [PubMed: 26729779]

18. Flensborg-Madsen T, Mortensen EL. Infant developmental milestones and adult intelligence: A 34-year follow-up. Early Hum Dev. 2015;91(7):393–400. [PubMed: 25981493]
19. Pidcock FS, Krishnan C, Crawford TO, Salorio CF, Trovato M, Kerr DA. Acute transverse myelitis in childhood: center-based analysis of 47 cases. Neurology. 2007;68(18):1474–1480. [PubMed: 17470749]
20. Defresne P, Hollenberg H, Husson B, et al. Acute transverse myelitis in children: clinical course and prognostic factors. Journal of child neurology. 2003;18(6):401–406. [PubMed: 12886975]
21. Chabas D, Castillo-Trivino T, Mowry EM, Strober JB, Glenn OA, Waubant E. Vanishing MS T2-bright lesions before puberty: a distinct MRI phenotype? Neurology. 2008;71(14):1090–1093. [PubMed: 18824673]
22. Wijnands JMA, Kingwell E, Zhu F, et al. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. Lancet neurology. 2017;16(6):445–451. [PubMed: 28434855]
23. Gorman MP, Golomb MR, Walsh LE, et al. Steroid-responsive neurologic relapses in a child with a proteolipid protein-1 mutation. Neurology. 2007;68(16):1305–1307. [PubMed: 17438221]
24. Hosseini B, Flora DB, Banwell BL, Till C. Age of onset as a moderator of cognitive decline in pediatric-onset multiple sclerosis. J Int Neuropsychol Soc. 2014;20(8):796–804. [PubMed: 25033163]
25. Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. Annals of neurology. 2000;48(6):885–892. [PubMed: 11117545]
26. Patti F Cognitive impairment in multiple sclerosis. Multiple sclerosis. 2009;15(1):2–8. [PubMed: 18805842]
27. Muckschel M, Beste C, Ziemssen T. Immunomodulatory treatments and cognition in MS. Acta Neurol Scand. 2016;134 Suppl 200:55–59. [PubMed: 27580907]
28. Majnemer A, Rosenblatt B. Reliability of parental recall of developmental milestones. Pediatr Neurol. 1994;10(4):304–308. [PubMed: 8068156]

Table 1:

Characteristics of the study sample

	Patients	Controls
Males/Females	153/308	215/209
Age at first event, mean ± SD (range) y	13.5 ± 3.8 (1.9 – 19.2)	
Age at first event (disease onset < 11), mean ± SD (range) y	7.1 ± 2.7 (1.9 – 10.9)	
Age at first event (disease onset ≥ 11), mean ± SD (range) y	15.1 ± 1.8 (11.1 – 19.2)	
Disease duration (time from first event to last event, mean ± SD (range) years	3.5 ± 2.8 (0.0 – 15.6)	

Table 2:

Developmental Milestones and Special Educational Services by Age at Onset

Registry Question	Total Responses	Disease Onset Age <11	Disease Onset Age ≥11	p-value
Walk after 15 months	9/407	3/81 = 3.7%	6/326 = 1.8%	0.39
Two word phrase after 24 months	9/368	3/76 = 4.0%	6/292 = 2.1%	0.39
Received special services prior to MS diagnosis	44/430	8/87 = 9.2%	36/343 = 10.5%	0.84
Child currently receives special education services	149/407	37/81 = 45.7%	112/326 = 34.4%	0.07
504 plan accommodations	107/414	26/82 = 31.7%	81/332 = 24.4%	0.20
Individualized education plans (IEP)	66/414	23/82 = 28.1%	43/332 = 13.0%	0.002
Occupational therapy	20/414	9/82 = 11.0%	11/332 = 3.3%	0.007
Physical therapy	39/414	11/82 = 13.4%	28/332 = 8.4%	0.20
Speech therapy	5/414	1/82 = 1.2%	4/332 = 1.2%	1.00
Reading assistance	32/414	15/82 = 18.3%	17/332 = 5.1%	0.0003
Math assistance	34/414	15/82 = 18.3%	19/332 =5.7%	0.001

For all cases and controls 22% were missing the two-word phrase response and 13% were missing the walking age response.

Table 3:

Disease onset prior to age 11 vs. Disease onset after age 11 modeled for special services

Special Service	OR	95% CI	P-value
504 Plan Accommodations	1.25	0.66, 2.34	0.49
Individualized Education Plans	2.00	1.00, 3.98	0.05
Occupational Therapy	4.12	1.43, 11.89	0.01
Physical Therapy	1.86	0.76, 4.54	0.17
Reading Assistance	2.73	1.12, 6.65	0.03
Math Assistance	3.13	1.36, 7.22	0.01
Speech Therapy	1.48	0.15, 14.36	0.74

Adjusted for disease duration, race/ethnicity, and mother's highest level of education Note: Speech therapy was not adjusted for mother's highest level of education due to small cell sizes