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Longitudinal Analysis of Developmental Delays in Children With Neurofibromatosis Type 1

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Abstract

Children with neurofibromatosis type 1 exhibit a variety of developmental delays. However, there is little information about the progression of these deficits over the course of development. Using the Parents' Evaluation of Developmental Status measurement tool, we assessed 124 infants (0-2 years of age), preschool-age children (3-5 years of age), and school-age children (6-8 years of age) with neurofibromatosis type 1 to define the natural history of delays. School-age children exhibited significantly more areas of delay than infants or preschool-age children. Delays in math, reading, gross motor, fine motor, and self-help development were observed more frequently in older than younger children. Finally, analysis of 43 subjects for whom longitudinal assessments were available revealed that children often migrated between delayed and nondelayed groups in all areas except gross motor development. Based on these findings, we advocate early developmental screening and intervention for this at-risk pediatric population, especially in the area of gross motor function.

Keywords

neurofibromatosis type 1, gross motor, development, fine motor, physical therapy

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Learning disabilities and cognitive impairments are common clinical problems in children with neurofibromatosis type 1,[1] affecting 30% to 65% of all children with this common neurogenetic disorder.[2–8] Previous studies have shown that the most common psychoeducational problems include visual-perceptual-motor delay and spelling and arithmetic disabilities.[4,9] There is also an increased prevalence of Attention deficit disorder and attention deficit hyperactive Disorder in this population.[10–13] In addition to these impairments, children with neurofibromatosis type 1 frequently demonstrate developmental delays.[12–17] We previously found that 68% of children with neurofibromatosis type 1 exhibited delays in at least 1 of 8 of the following areas: fine motor, gross motor, receptive language, expressive language, math/pre-math, reading/pre-reading, self-help, and social-emotional development.[17] Similarly, other reports on toddlers (aged 21-30 months) with neurofibromatosis type 1 established that these delays often present early in development.[15] However, these studies examining developmental delays in children with neurofibromatosis type 1 have focused on specific age groups, and have generally assessed a single delay or a single age cohort. In this regard, less is known about the age-dependent appearance and progression of these delays during childhood. In the current study, we sought to determine the age of presentation for specific areas of delay in children with neurofibromatosis type 1 and the time-dependent progression of these deficits.

Materials and Methods

Participants

This study was conducted under an approved Human Studies Protocol at the Washington University School of Medicine using a waiver of informed consent. One hundred seventy-five assessments were administered to children younger than 8 years as part of their routine clinical care at the St. Louis Children's Hospital Neurofibromatosis Clinical Program between February 2010 and July 2012. Diagnoses of neurofibromatosis type 1 were established by clinical assessment. Of the 175 assessments, 124 were first assessments, 43 were second assessments, and 8 were third assessments. In total, longitudinal data

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were available for 43 unique subjects. To maintain consistency across the longitudinal data set, we defined follow-up assessment analysis as the changes observed between the first and second visits. Follow-up assessments were analyzed separately from initial assessments. Four patients who did not have a confirmed diagnosis of neurofibromatosis type 1 based on the National Institutes of Health Consensus Development Conference criteria were excluded from the study.[18] No families refused screening.

Developmental Assessment

The Parents' Evaluation of Developmental Status: Developmental Milestones evaluates expressive language, receptive language, fine motor, gross motor, social-emotional, self-help, reading/pre-reading, and math/pre-math for age-appropriate achievement. The 20 assessment forms included in the evaluation tool vary in difficulty and correspond to evaluations for 20 different age groups. Many of the assessment questions for infants and young children were directed to parents in order to determine what tasks their children could perform. In most cases, the total required time for test administration was less than 5 minutes. Children with performance scores below the 16th percentile on any particular section were considered delayed in that area. The screening tool was developed based on the Brigance Inventory of Early Development II and the Brigance Comprehensive Inventory of Basic Skills–Revised, which has a sensitivity of 70% and a specificity of 95% across domains and age levels.[19]

Cohort Analysis

Subjects were segregated into 3 age-defined cohorts based on age: Infant (0-2 years of age, 44 subjects), Preschool (3-6 years of age, 54 subjects), and School (6-8 years of age, 26 subjects) groups. Total areas of delay were evaluated for each cohort, 95% confidence intervals were calculated, and Kruskal-Wallis calculations were performed to determine significance. Age-defined cohorts were analyzed using the Fisher's exact test to determine significant differences in developmental achievement between age cohorts. All analyses were 2-sided, and significance was set at a P value of .05. Statistical analyses were performed using SAS (SAS Institutes, Cary, North Carolina).

Longitudinal Analysis of Developmental Delays

From the records of the 43 subjects with longitudinal data available, total areas of delay were evaluated for both initial and follow-up assessments, and 95% confidence intervals were calculated. The McNemar's test was used to assess paired data with regard to the presence of delays from initial to second assessment.

Results

Analysis of the total delays revealed that the percentage of areas delayed over time increased as a function of age, with a mean percentage of areas delayed of 22%, 28%, and 47% for the infant, preschool, and school-age cohorts, respectively (Figure 1, $P = .002$). Aside from receptive language, assessments across developmental areas showed increasing prevalence with age across delay areas (Figure 2). Significant differences in specific delays were found between the different age groups, including math/pre-math ($P < .001$), reading/pre-reading ($P = .008$), gross motor ($P = .001$), fine motor ($P = .016$), and self-help development ($P = .010$). Twenty-five percent (2/8) of infants, 17% (8/47) of preschool-age children, and 62% (16/26) of school-age children tested positive for delays in math/pre-math. For reading/pre-reading,

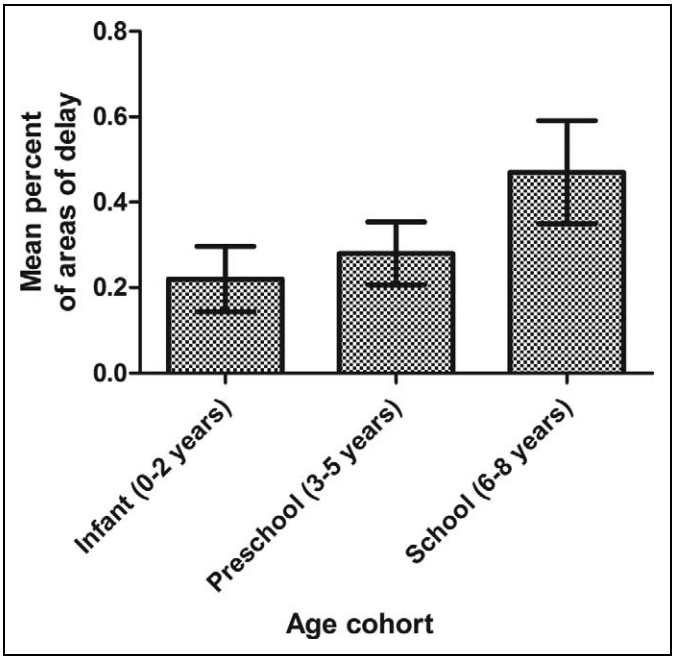

Figure 1. Total delays by age cohort in children with neurofibromatosis type 1. The mean percentages of areas of delay in children with neurofibromatosis type 1 are shown for each age group. The mean and 95% confidence interval are included. School-age children exhibited a greater percentage of delays compared to infants and preschool children ($P = .002$).

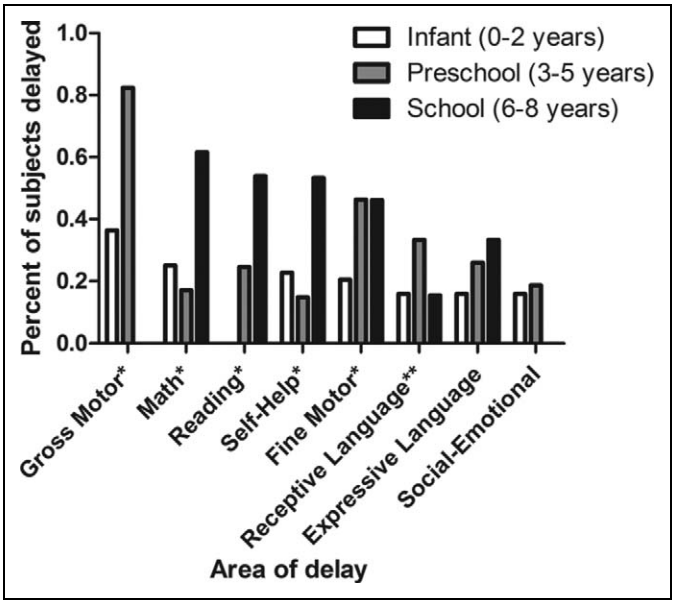

Figure 2. Specific delays by age in children with neurofibromatosis type 1. The percentage of subjects delayed in each area is shown as a function of age. *$P = .046$; **$P = .081$.

Table 1. Total Areas of Delay at Initial and Follow-Up Assessment

	Mean	Median	95% CI upper bound	95% CI lower Bound	*P* value
Percentage of total areas with delay on initial assessment	26	17	34	18	.081
Percentage of total areas with delay on follow-up assessment	32	17	41	23	

Table 2. Specific Areas of Delay on Initial and Follow-Up Assessment

		Follow-up assessment			
Area	Initial assessment	Delay absent	Delay present	*P* value	N
Gross motor	Delay absent	3	4	.0455	12
	Delay present	0	5		
Fine motor	Delay absent	20	10	.1967	43
	Delay present	5	8		
Receptive language	Delay absent	20	10	.4054	43
	Delay present	5	8		
Expressive language	Delay absent	21	11	.2253	39
	Delay present	6	1		
Math/pre-math	Delay absent	17	7	.2059	29
	Delay present	3	2		
Reading/pre-reading	Delay absent	21	3	.3173	28
	Delay present	1	3		
Self-help	Delay absent	24	5	1.0000	39
	Delay present	5	5		
Social-emotional	Delay absent	18	2	.5637	26
	Delay present	1	5		

25% (13/53) of preschool-age children and 54% (14/26) of school-age children exhibited delays. Reading/pre-reading was not evaluated in children in the infant cohort. Gross motor testing was the area of delay with the greatest percentage of children affected. Thirty-six percent (16/44) of infants and 82% (14/17) of preschool-age children had gross motor delays; however, school-age children were not tested in this specific area. Fine motor delays were detected in 20% (9/44) of infants, 46% (25/54) of preschool-age children and 46% (12/26) of school-age children. Self-help delays showed a substantial increase in prevalence in school-age children: These delays were detected in 23% (10/44) of infants, 15% (8/54) of preschool-age children, and 53% (8/15) of school-age children. In addition, marginally significant differences in receptive language development were detected ($P = .085$). Receptive language was the only area of delay that showed modest improvements in percentage of subjects delayed with increasing age. Sixteen percent (7/44) of infants, 33% (18/54) of preschool-age children, and 15% (4/26) of school-age children presented with receptive language delays.

Of the 43 subjects with longitudinal assessments, analysis of total areas of delay for both the initial and follow-up assessments showed that for the same children, there was a marginally significant increase in delays ($P = .081$, Table 1). Importantly, children often migrated between delayed and nondelayed groups from year to year, and frequently became delayed in a greater number of areas on follow-up evaluation (Table 2). The only area of delay observed in all age groups was in gross motor development ($P = .046$).

Discussion

In the current study, we used a single measurement tool to define age-dependent development and evolution of common delays in children with neurofibromatosis type 1. First, we found that both gross and fine motor delays are typically detected in children between 3 and 5 years of age. In the general population, however, there is not a consistently reported time of onset for motor delays.[20] Although the American Academy of Pediatrics recommends 9-, 18-, and 30-month screening for children,[21] we suggest that screening for children with neurofibromatosis type 1 should continue at least through 5 years of age.

Second, academic-related performance delays tended to present at later ages. In this regard, 7 of 24 subjects without math/pre-math delays at initial presentation exhibited delays at follow-up assessment, and 3 of 24 subjects without initial reading/pre-reading delays were found to have delays at follow-up assessment. The temporal pattern of motor delay preceding academic delay has been previously described in the general pediatric population[22] but had not been previously reported in children with neurofibromatosis type 1. Importantly, in children without neurofibromatosis type 1, there is a significant predictive relationship between gross motor development and performance on subtests of working memory and processing speed.[22] As such, we predict that through early screening and intervention for gross motor delays, the prevalence of academic delays may consequently decrease.

Third, in children with neurofibromatosis type 1, gross motor delays do not improve over time. The persistence of this specific delay throughout all age groups and their correlation with future academic performance support the implementation of early motor screens for all children with neurofibromatosis type 1. Previous studies have demonstrated that early interventions for children with developmental disabilities can promote greater achievement of functional potential later in life.[23,24] Although we did not directly evaluate the impact of therapy services on neurofibromatosis type 1–associated motor delays, regular and intensive therapy provides benefit to children with severe developmental delays.[24] Studies are planned to specifically address the efficacy of targeted therapy services for children with neurofibromatosis type 1.

There are several limitations inherent in our study. It should be noted that the Parents' Evaluation of Developmental Status: Developmental Milestones tool does not evaluate each developmental area uniformly across age groups, making small sample sizes an issue for longitudinal analysis across certain delay areas. In this regard, gross motor delays are not tested for children in the school-age cohort, thus limiting our ability to identify these delays in children older than 6 years of age. To circumvent this problem, we have recently begun to employ the more extensive Bruininks-Oseretsky Test of Motor Proficiency, which provides a validated tool for motor testing of children between the ages 4 and 21. In addition, we appreciate that there are fewer longitudinal data available for analysis, partly because of patient attrition and maturation beyond the upper extremes of age for which the test is validated.

Conclusion

Children with neurofibromatosis type 1 are at an increased risk for variety of developmental delays, which limit their overall academic performance. To define the natural history of specific developmental delays in young children with neurofibromatosis type 1, we examined the age-dependent presentation and progression of these deficits. We found that greater areas of delay were observed in school-age children relative to younger children, specifically those in the areas of math, reading, gross motor, fine motor, and self-help development. In addition, substantial gross motor delays were identified in all age groups evaluated. Based on these findings and prior reports examining children with other developmental disabilities, the prompt recognition of developmental delays affords an opportunity to initiate interventional therapy aimed at improving future academic success in this at-risk pediatric population.

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Author Contributions

LEW performed the data analysis and wrote the first drafts of the manuscript. FG performed the statistical analyses. CMD performed the clinical assessments. DHG performed the final editing of 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.

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Ethical Approval

This study was conducted under an approved Human Studies Protocol at the Washington University School of Medicine using a waiver of informed consent.

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