Developmental Trajectories of Young Children with Neurofibromatosis Type 1: A Longitudinal Study from 21 to 40 Months of Age

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Objective To establish the developmental trajectory of young children with neurofibromatosis type 1 (NF1) during the first 4 years of life.

Study design In this longitudinal study, 39 children with NF1 and 39 controls were assessed with the Bayley Scales of Infant Development, Second Edition at 21 (time point 1, or T1) and 30 months (T2) of age, and the Wechsler Preschool and Primary Scale of Intelligence, Third Edition at 40 months (T3). Language was also assessed at T2 and T3. Parents rated their child's productive vocabulary at T1 and T2, and behavior at each time point. Linear mixed models were performed to examine cognitive development and behavior over time. Linear regressions were conducted to determine whether mental development and productive vocabulary at T1 or T2 predicted intellectual and language outcomes at T3.

Results Over time, the NF1 group had significantly lower cognitive scores than controls. Parent ratings indicated no group differences in behavior at each time point. Earlier mental function significantly predicted later general intelligence. Earlier productive vocabulary was a significant predictor of later language skills.

Conclusions There are consistent differences over time in cognitive performance between children with NF1 and unaffected peers during the early childhood period. Earlier mental function and productive vocabulary are significant predictors of subsequent general intelligence and performance on language measures in NF1. This provides an opportunity for early identification and treatment for young children with NF1 who may show signs of impairments in these developmental domains. *(J Pediatr 2015;166:1006-12)*.

Neurofibromatosis type 1 (NF1) is an autosomal-dominant neurogenetic condition with a birth incidence of 1 in 2712.[1] Cross-sectional studies of children with NF1 have shown impairments in attention, visual perception, language, executive function, academic skills, and behavior.[2,3] Few studies in NF1 have focused on time-dependent cognitive progression from late childhood to adulthood.[4-6] One study has reported on the developmental progression of younger children with NF1 (0-8 years of age).[7] On the basis of parental report, children shifted between delays and typical performance from year to year. Children often became delayed in language and pre/academic skills at follow-up.[7]

An important aspect of pediatric follow-up is to determine whether developmental functioning in toddlerhood can predict later neurodevelopmental performance. This information can define early developmental skills that are necessary for later intellectual growth.[8,9] In the general population, there is evidence that mental development at age 2 is a reliable predictor of intelligence at the third and fourth year.[10] For at-risk pediatric groups, a recent meta-analysis found that earlier mental function was significantly predictive of later intelligence.[11] In addition, findings indicate that productive vocabulary at 2 years of age is predictive of language function at age 3 in typically developing samples.[12]

The aims of the present study were to follow the cognitive and behavioral trajectories of young children with NF1 and healthy unaffected peers at 21 months (time point 1 or T1), 30 months (T2), and 40 months of age (T3) with the use of standardized assessments and parental report. We also sought to determine whether mental function and productive vocabulary at T1 or T2 predicted cognitive and language skills at T3. Our hypotheses were that: (1) young children with NF1 will have lower cognition than healthy peers over time; (2) toddlers with NF1 will demonstrate lower behavioral regulation than

BSID-II	Bayley Scales of Infant Development, Second Edition	SES	Socioeconomic status
		T1	Time point 1
		T2	Time point 2
FSIQ	Full Scale IQ	T3	Time point 3
GLC	Global Language Composite	TABS	Temperament and Atypical Behavior Scale
MacArthur CDI	MacArthur Communicative Development Inventories – Words and Sentences	WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence Australian Adaptation, Third Edition
MDI	Mental Development Index		
NF1	Neurofibromatosis type 1		

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controls over time; (3) mental development scores at T1 or T2 are predictive of general intelligence at T3; and (4) productive vocabulary scores at T1 or T2 are predictive of language performance at T3.

Methods

Children who fulfilled the diagnostic criteria for NF1 specified by the National Institutes of Health were recruited from the Neurogenetics Clinic, The Children's Hospital at Westmead, Sydney, Australia.[13] A pediatric neurologist or geneticist confirmed the diagnosis of NF1 for each child. There were 3 options to recruit control children: unaffected siblings of children with nonfamilial NF1 attending the Neurogenetics Clinic who did not have a sibling participating in the study; children attending private preschools or child care centers in the Sydney metropolitan area; and study advertisements placed in local community newspapers. In this study, all controls were recruited through preschools and newspaper advertisements. Children with other medical conditions, including visual/hearing loss or intracranial pathology, were excluded. Parents were required to be fluent in English and children were monolingual (English) speakers.

Families who were eligible to take part were mailed a study information sheet. A follow-up telephone call was made to determine the family's interest in the study. Informed signed consent was obtained from all participants. Each child had a comprehensive developmental assessment with the same psychologist at all three time points. At each assessment, parents completed a questionnaire about their child's behavior. We have previously reported cross-sectional results from some of these children.[2,14] This study was approved by The Children's Hospital at Westmead Ethics Committee.

The Bayley Scales of Infant Development, Second Edition (BSID-II) Mental Development Index (MDI) score was used at T1 and T2 to assess mental development.[15] The Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Australian Adaptation (WPPSI-III) was administered at T3 to determine general intelligence.[16] Parents completed the MacArthur Communicative Development Inventories – Words and Sentences (MacArthur CDI) at T1 and T2 to determine the total number of single words their child produced (Productive Vocabulary).[17] At T2, children's basic vocabulary skills were assessed with the WPPSI-III Receptive Vocabulary and Picture Naming subtests, with a Global Language Composite (GLC) calculated.[16] At T3, the Sentence Repetition and Verbal Fluency subtests from the Developmental Neuropsychological Assessment were administered.[18]

At T3, the Letter-Word Identification subtest from the Woodcock-Johnson Tests of Achievement, Third Edition was administered.[19] From T1 to T3, parents completed the Temperament and Atypical Behavior Scale (TABS).[20] A TABS Temperament and Regulatory Index score was calculated, with greater Temperament and Regulatory Index scores indicative of a greater risk for temperament difficulties. The socioeconomic status (SES) of both parents (ie, educational level and current occupation) was determined with the Hollingshead Four-Factor Index of Social Status.[21] Continuous SES scores range from 8 (low) to 66 (high).

Statistical Analyses

Data were analyzed using SPSS version 21 (IBM, Armonk, New York). Asymmetrically distributed data are reported as median and IQR. An independent samples t test was conducted to examine differences between the groups for parental SES. A significance level of $P = .05$ was used.

A linear mixed model was performed to examine the cognitive development from T1 to T3 and compare differences between groups. Previous research in NF1 has shown that parental SES and sex is associated with cognitive performance,[22] so these variables were included in the model. Another predictor was time point, which was represented as a categorical variable to account for the fact that different tests were administered at the time points (ie, MDI at T1, MDI at T2, Full Scale IQ [FSIQ] at T3). Group status (NF1, control) also was included as a fixed effect to examine the difference between the NF1 and control groups. Because of the sample size, a limited number of interactions were included: group status by parental SES, group status by sex, and group status by time point. The mixed models procedure was repeated to examine the changes in atypical behavior (TABS) from T1 to T3.

Separate multiple linear regressions (forced entry) were calculated to determine which earlier time point (MDI at T1 or T2) had a greater influence in predicting FSIQ at T3. Other predictors in the regression model included parental SES, sex, and group status. In addition, the following interactions were included to determine whether there were differences between the NF1 and control group: group status by MDI (ie, at T1 or T2 when predicting FSIQ), group status by parental SES, and group status by sex. The linear regression procedure also was repeated to determine the ability of MacArthur CDI Productive Vocabulary scores at T1 or T2 to predict language performance at T3. For significant predictors, the standardized beta coefficients were visually inspected to identify which had the greatest influence in predicting the outcome. The MacArthur CDI at T2 predicting GLC at T3 regression model was run using mean-centered variables, due to collinearity. The following predictor variables were centered: parental SES, MacArthur CDI at T2, group by parental SES, and group by MacArthur CDI at T2.

Results

Longitudinal data were available for 39 children with NF1 and 39 control participants. The NF1 group consisted of 26 (67%) sporadic cases and 13 (33%) familial cases. Each group comprised 16 (41%) female and 23 (59%) male subjects. These children completed all 3 scheduled assessments. However, there were minimal missing data (≤5%), as a few of the children were unable to complete certain tests because of poor cooperation, distractibility, and/or fatigue; hence, a test score could not be calculated. Some parents also partially completed or did not return the