Cognitive Features that Distinguish Preschool-Age Children with Neurofibromatosis Type 1 from Their Peers: A Matched Case-Control Study

Jennifer Lorenzo, MPsych[1,2], Belinda Barton, PhD[2,3], Shelley S. Arnold, BA[1], and Kathryn N. North, MD[1,2,4,5]

Objective To examine the cognitive functioning of 40-month-old children with neurofibromatosis type 1 (NF1).

Study design In this case-control study, 43 children with NF1 and 43 comparison children (matched by age, sex, and maternal years of education) were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition. Language, visual perception, preliteracy, and executive functioning were also examined. Parents completed questionnaires about their child's behavior. Group differences were examined using the paired-samples *t* test or the related Wilcoxon signed rank test. Conditional logistic regression was conducted to identify which cognitive variables predicted group membership (ie, NF1 or control).

Results The NF1 group had significantly poorer general intelligence than matched comparisons. Preschool-age children with NF1 had significantly poorer language, visual perception, response inhibition, and preliteracy skills than comparison children. The Wechsler Preschool and Primary Scale of Intelligence, Third Edition, Object Assembly and Information subtests were significant predictors of group membership. Parent ratings indicated no group differences in behavior.

Conclusions After accounting for potentially confounding variables of age, sex, and maternal years of education, young children with NF1 have significantly poorer intellectual functioning, expressive language, and visual perception. These cognitive features that distinguish young children with NF1 from healthy peers can be detected in the preschool age group and are likely to impact on learning and performance during early school years. These areas should be targeted for intervention to maximize the developmental outcomes of young children with NF1. *(J Pediatr 2013;163:1479-83)*.

Neurofibromatosis type 1 (NF1) is a common single gene disorder characterized by cutaneous, ophthalmologic, and orthopedic features, such as café-au-lait macules, cutaneous neurofibromas, iris hamartomas, optic pathway tumors, developmental bony defects, and scoliosis.[1] Apart from physical manifestations, NF1 is associated with a high frequency of cognitive dysfunction in middle to late childhood.[2] Approximately 80% of school-aged children with NF1 demonstrate deficits in 1 or more areas of cognition, including attention, visual perception, executive function, expressive and receptive language, reading, spelling, and mathematics.[2] Cognitive impairment can also be detected in children with NF1 prior to school age. Over 30% of 2½-year-old children with NF1 demonstrate a mildl delay in mental development.[3] Approximately 68% of 4½ year olds with NF1 show expressive and/or receptive language difficulties.[4]

Individual and environmental factors can contribute to a child's cognitive outcomes. In the general population, the heritability of children's intelligence can be influenced by socioeconomic status (SES).[5] In children with NF1, SES has also been found to significantly correlate with general intelligence—with those who are from a lower SES background more likely to have lower Full Scale IQ scores.[2] Another factor that may impact on a child's cognitive performance is sex. In the general population, there is a higher prevalence of learning disabilities among boys.[6] This could be due to faster maturational rates in females and/or sex differences in linguistic and spatial information processing.[6] Sex effects have also been reported in NF1, with more males being diagnosed with a specific learning disability than females.[2]

The vast majority of studies to date of the NF1 cognitive phenotype have focused on school-aged children with NF1 and have reported a slight lowering of IQ scores.[7] These studies have often utilized pairwise NF1-unaffected sibling comparisons.[7] We examined the cognitive skills of 40-month-old children with NF1 by utilizing a case-control design, which individually matches each child with NF1 to a healthy comparison child by SES (ie, maternal years of education),

BASC-II	Behavior Assessment System for Children, Second Edition
BRIEF-P	Behavior Rating Inventory of Executive Function, Preschool Version
EOWPVT	Expressive One-Word Picture Vocabulary Test
NEPSY	Developmental Neuropsychological Assessment
NF1	Neurofibromatosis type 1
SES	Socioeconomic status
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition

From the [1]Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead; [2]Discipline of Pediatrics and Child Health, Faculty of Medicine, University of Sydney; [3]Children's Hospital Education Research Institute, The Children's Hospital at Westmead, New South Wales, Australia; [4]Murdoch Children's Research Institute, The Royal Children's Hospital; and [5]Department of Pediatrics, University of Melbourne, Victoria, Australia

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sex, and age. A matched case-control design allows us to distinguish differences in cognitive performance that are more likely to be due to the presence of the NF1 gene. We hypothesized that 40-month-old children with NF1 will have significantly poorer general intelligence and demonstrate significantly poorer performance on specific cognitive measures than healthy matched comparison children.

Methods

Children with NF1 who satisfied the National Institutes of Health diagnostic criteria[8] were recruited from the Neurogenetics Clinic, The Children's Hospital at Westmead, Sydney, Australia. A pediatric geneticist or neurologist confirmed the diagnosis of NF1. The children were enrolled in an ongoing longitudinal study involving regular neurodevelopmental assessments up to 7 years of age. Cross-sectional data obtained at the 40-month scheduled assessment is presented here. Comparison children (individually matched by age, sex, and maternal years of education) were recruited by the following means: unaffected siblings of children with sporadic NF1 attending the Neurogenetics Clinic who did not have a sibling enrolled in the study, children attending private preschools in the Sydney metropolitan area, and advertisements placed in local community newspapers. Children with other medical conditions, such as intracranial pathology and visual or hearing loss were excluded. Parents were required to be fluent in English, and all children were monolingual (English) speakers.

The study was approved by The Children's Hospital at Westmead Ethics Committee. Eligible families that attended the Neurogenetics Clinic were sent a study information sheet. A follow-up phone call was made to ascertain the family's interest to enroll in the study. Informed signed consent was obtained from all participants. Each child had a developmental assessment, which was conducted by a psychologist at the hospital. Parents were also invited to complete questionnaires about their child's development.

General intellectual functioning was assessed with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III), Australian Adaptation.[9]

Basic expressive vocabulary was assessed with the Expressive One-Word Picture Vocabulary Test (EOWPVT).[10] The Sentence Repetition subtest from the Developmental Neuropsychological Assessment (NEPSY) examined the child's ability to repeat sentences.[11] Rapid word generation skills were assessed with the NEPSY Verbal Fluency subtest.[11]

Letter knowledge was assessed with the Letter-Word Identification subtest from the Woodcock-Johnson Tests of Achievement, Third Edition.[12]

Copying of line drawings was evaluated by the Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition.[13]

Visual selective attention was assessed with the Visual Attention subtest from the NEPSY.[11] The *Conners' Attention Deficit Hyperactivity Disorder/Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Scales Parent Version was used to assess parents' perceptions of their children's risk of attention problems.[14]

Spatial planning/organization skills were assessed by the Tower of Hanoi.[15] Response inhibition was evaluated using the Shape School (conditions A and B).[16] Nonverbal working memory was assessed by the Delayed Alternation.[17] Parents completed the Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P), to provide information about their child's executive skills.[18] Parents completed the Behavior Assessment System for Children, Second Edition (BASC-II), Preschool Version.[19] Maternal years of education was categorized into 4 domains using a modified version of the Hollingshead Four-Factor Index of Social Status.[20] SES of both parents (ie, educational level and occupation) was determined using the same measure. Categorical and corresponding continuous scores are 1 high SES (66-55), 2 (54-40), 3 (39-30), 4 (29-20), and 5 low SES (19-8).

Statistical Analyses

Data was analyzed using SPSS v 19 (SPSS Inc, Chicago, Illinois). Asymmetrically distributed data are reported as median and IQR. Differences between the 2 groups for continuous variables were examined using the paired-samples *t* test or the related samples Wilcoxon signed rank test when scores were asymmetrically distributed.

Further, to determine which variables predicted group membership (NF1 or comparison child), a conditional logistic regression analysis (backward stepwise method) was conducted. Single domain or subtest scores rather than global scores (eg, Full Scale IQ) were used to assist in identifying specific features that distinguished the 2 groups. Because there were no a priori assumptions, possible predictor variables were identified as being those with a large effect size ($\geq$0.60) between the 2 groups. Effect sizes were calculated for normally distributed data using the mean scores of both groups divided by the pooled standard deviation (Cohen's *d*), and effect sizes for non-normally distributed data were calculated as the z score divided by the square root of the sample size.[21] For the BRIEF-P and BASC-II, only composite or index scores were analyzed to control the type I error rate. In addition, the Holm procedure (a modified Bonferroni procedure) was applied to control the type I error rate.

A total of 43 matched pairs were assessed. However, there is some missing data because a few children were unable to complete testing due to poor cooperation, distractibility, and/or fatigue; hence, a score could not be calculated. Some parents also partially completed or did not return the questionnaires. In addition, as it was a case-control design, if data were unavailable for either the NF1 or comparison child, the matched individual could also not be included in the analyses.

Results

The mean age of the NF1 group was 40.23 months (SD = 0.72) and 40.16 months (SD = 0.48) for the comparison group. The NF1 group comprised of 25 sporadic cases