Executive Function and Adaptive Behavior in Muenke Syndrome

Colin M. P. Yarnell, BA[1,*], Yonit A. Addissie, BA[1,*], Donald W. Hadley, MS[1], Maria J. Guillen Sacoto, MD[1], Nneamaka B. Agochukwu, MD[1], Rachel A. Hart, BS[1], Edythe A. Wiggs, PhD[1], Petra Platte, PhD[2], Yvonne Paelecke, PhD[2], Hartmut Collmann, MD[3], Tilmann Schweitzer, MD[4], Paul Kruszka, MD, MPH[1], and Maximilian Muenke, MD[1]

Objective To investigate executive function and adaptive behavior in individuals with Muenke syndrome using validated instruments with a normative population and unaffected siblings as controls.

Study design Participants in this cross-sectional study included individuals with Muenke syndrome (P250R mutation in *FGFR3*) and their mutation-negative siblings. Participants completed validated assessments of executive functioning (Behavior Rating Inventory of Executive Function [BRIEF]) and adaptive behavior skills (Adaptive Behavior Assessment System, Second Edition [ABAS-II]).

Results Forty-four with a positive *FGFR3* mutation, median age 9 years, range 7 months to 52 years were enrolled. In addition, 10 unaffected siblings served as controls (5 males, 5 females; median age, 13 years; range, 3-18 years). For the General Executive Composite scale of the BRIEF, 32.1% of the cohort had scores greater than +1.5 SD, signifying potential clinical significance. For the General Adaptive Composite of the ABAS-II, 28.2% of affected individuals scored in the 3rd-8th percentile of the normative population, and 56.4% were below the average category (<25th percentile). Multiple regression analysis did not identify craniosynostosis as a predictor of BRIEF (P = .70) or ABAS-II scores (P = .70). In the sibling pair analysis, affected siblings performed significantly poorer on the BRIEF General Executive Composite and the ABAS-II General Adaptive Composite.

Conclusion Individuals with Muenke syndrome are at an increased risk for developing adaptive and executive function behavioral changes compared with a normative population and unaffected siblings. *(J Pediatr 2015;167:428-34)*.

Craniosynostosis occurs in approximately 1 in 2000 live births and is characterized by the premature fusion of one or more cranial sutures resulting in malformation of the skull.[1] Potential consequences of abnormal skull growth include increased intracranial pressure, problems with hearing and vision, impaired blood flow in the cerebrum, and developmental delay.[2,3] Muenke syndrome (OMIM 602849) constitutes the most common syndromic form of craniosynostosis, with an incidence of 1 in 30 000 births; 8% of patients with craniosynostosis manifest Muenke syndrome.[2,4,5]

Muenke syndrome is defined by the presence of a c.749 C>G *FGFR3* mutation encoding a P250R substitution in the fibroblast growth factor receptor 3 protein, 1 of 4 tyrosine kinase receptors that bind fibroblast growth factors.[6,7] *FGFR3* is expressed during brain development, but its role in cognitive and behavioral phenotypes remains largely unknown.[8,9]

The classic presentation of Muenke syndrome includes unilateral or bilateral coronal suture craniosynostosis, broad thumbs and toes, carpal and tarsal fusions, hearing loss, and seizures. In recent years, evidence of cognitive and behavioral differences in persons with Muenke syndrome has surfaced, yet research on this topic remains preliminary.[10-15] There is also evidence suggesting that social and attention problems are more prevalent in Muenke syndrome than in the normative population or in other craniosynostosis syndromes[15,16]; however, studies on the cognitive, emotional, and behavioral component of the syndrome have included only small numbers of patients and used various tools to assess behavior and cognitive abilities. Our growing collection and experience with families known to carry the *FGFR3* mutation associated with Muenke syndrome has generated increasing interest in exploring the broad spectrum of phenotypes associated with the mutation, particularly the social and behavioral phenotypes.

The present study made use of standardized tests, including the Behavior Rating Inventory of Executive Function (BRIEF) and the Adaptive Behavior Assessment System, Second Edition (ABAS-II), to evaluate executive function and adaptive behaviors in individuals affected with Muenke syndrome. Executive function has been defined as "a set of interrelated functions that are responsible

ABAS-II	Adaptive Behavior Assessment System, Second Edition
ADHD	Attention deficit hyperactivity disorder
BRIEF	Behavior Rating Inventory of Executive Function
FSIQ	Full-scale IQ
GAC	Global Adaptive Composite
GEC	Global Executive Composite

From the [1]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD; [2]Department of Psychology I, Institute of Psychology, University of Würzburg; and [3]Section of Pediatric Neurosurgery, Department of Neurosurgery, and [4]Department of Orthodontics, University Hospital of Würzburg, Würzburg, Germany

*Contributed equally.

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for purposeful, goal-directed, problem solving behavior."[17] These functions are instrumental in the process of intentionally directing or controlling one's own behavior to achieve a certain goal or solve a problem, and include such abilities as planning and organizing a way to solve problems, initiating behavior, inhibition (controlling impulses), goal-setting, monitoring and evaluating behavior, as well as shifting from one situation or aspect of a problem to another.[17]

In contrast, adaptive behavior entails a collection of age-appropriate skills that are needed to "adapt to" or to function independently in one's environment. Adaptive skills are practical, everyday skills needed for "effectively and independently taking care of oneself and interacting with other people."[18]

Methods

The study was approved by the National Human Genome Research Institute Institutional Review Board (05-HG-0131) at the National Institutes of Health in Bethesda, MD. Participants had molecular testing and individuals carrying the *FGFR3* P250R mutation were considered affected. Each participant or a legal guardian provided informed consent to participate in the study. Participants completed a series of assessments and questionnaires in 1 of 3 ways: over the phone, in person at our Bethesda campus, or online via a website created for our study (http://muenkesyndrome.nhgri.nih.gov). Response of participants electing to complete the forms online were recorded within a secure database.

Testing

Executive function was assessed using the BRIEF with a license to use on our website purchased through Psychological Assessment Resources, Inc (www.parinc.com). The BRIEF measures the construct of executive function in all ethnicities, age 2-90 years.[17] The 4 versions of the BRIEF correspond to different age groups and respondents: BRIEF, BRIEF-P (preschool version), BRIEF-SR (self-report version), and BRIEF-A (adult version). We chose to use BRIEF-P for children aged 2-5 years, BRIEF for children aged 5-18 years (parent or teacher forms), and BRIEF-A for adults aged 18-90 years (self-report or informant report forms). All versions of the assessment produce clinical scales labeled Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize, as well as a Global Executive Composite (GEC), which is a summary score incorporating all clinical scales. Raw scores were converted into scaled and standard scores based on age and sex (*T* scores). For the normative population, the mean (*T* score) is 50 and the SD is 10. A higher score indicates poorer executive function. BRIEF *T* scores are subdivided into 3 categories: "average" scores <60 (<+1 SD), scores ranging from 60 to 64 (≥+1 SD and <+1.5 SD), and scores ≥65 (≥+1.5 SD). According to the BRIEF manual, *T* scores of ≥65 are considered abnormally elevated and to have potential clinical significance.[19] An inconsistency scale was used to evaluate the validity of the data and indicated the extent to which the respondent answered similar BRIEF items in an inconsistent manner. If a participant's answers were scored as "inconsistent," then that participant's data were excluded from the analysis.

Adaptive behavior was assessed with the ABAS-II with a license for use on our website purchased through Western Psychological Services (wpspublish.com). The ABAS-II is a tool designed to measure the adaptive behavior of individuals of all ethnicities aged 0-89 years.[18] There are 3 age groups and 3 response forms: a parent/primary caregiver form for young children aged 0-5 years, a parent form for respondents aged 5-21 years, and an adult form for respondents aged 16-89 years. The ABAS-II includes composite scores for conceptual, social, and practical domains, as well as a Global Adaptive Composite (GAC). Raw scores were converted into standardized *T* scores based on age. The normative population's mean *T* score is 100 and the SD is 15. A lower score signifies worse adaptive behavior. According to the ABAS-II manual, scores are divided into the following categories based on percentile (%) of the normative population: very superior, >130 (≥98%); superior, 120-129 (91%-97%); above average, 110-119 (75%-90%); average, 90-109 (25%-74%); below average, 80-89 (9%-24%); borderline, 71-79 (3%-8%); extremely low, ≤70 (≤2%).

Along with collecting data on executive functioning and adaptive behavior, the study also collected data on participants' medical, family, and school/work histories. Mutation status for all participants was determined from Clinical Laboratory Improvement Act of 1988–approved *FGFR3* mutation testing.

Statistical Analyses

Data analyses were performed using R version 3.1.2 (R Institute for Statistical Computing, Vienna, Austria) and Microsoft Excel for Mac 2011, version 14.4.5 with StatPlus:mac V5 (Microsoft, Redmond, Washington). Total cohort *FGFR3* P250R positive participant means and SDs were calculated for the ABAS-II and BRIEF domains and compared with normative populations. In addition, ABAS-II and BRIEF means were compared between probands and their age- and sex-matched, mutation-negative siblings; significance was evaluated using paired *t* tests. Affected and unaffected siblings were paired based on lowest difference in age. By chance, all but 1 sibling pairs were the same sex. Effect size, using Cohen dz, was determined by comparing affected individuals (the group with unaffected siblings) with unaffected siblings.

Multiple regression analysis was performed using the BRIEF or ABAS-II score as the dependent variable and sex, age, seizure history (at least 1 reported seizure), craniosynostosis presence, craniosynostosis surgery history, developmental delay, and hearing loss as independent variables. In addition, family identification as an independent variable was used to evaluate whether large families affected outcomes.

Results

Participants in our study (**Table I**) included a total of 44 affected individuals (21 males, 23 females); median age was

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