Acquired Autistic Behaviors in Children with Mucopolysaccharidosis Type IIIA

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Objectives To assess autism spectrum disorder (ASD) behaviors in children with mucopolysaccharidosis type IIIA (MPS IIIA) using a standard measure, understand the behavioral evolution of the disease, and provide specific guidelines for diagnosis.

Study design Children (n = 21) with documented enzyme deficiency and *SGSH* gene mutations, cognitive age-equivalent >12 months, and early onset were administered the Autism Diagnostic Observation Schedule (ADOS) (module 1) and Bayley Scales of Infant Development–Third Edition. ADOS Social Affect and Restricted Repetitive Behavior total scores, as well as Bayley Scales of Infant Development–Third Edition cognitive age-equivalent scores, are reported using descriptive statistics and graphic presentations.

Results Thirteen of the 21 children evaluated met the ADOS criteria for ASD/autism. ADOS score was strongly associated with age; all 11 children aged >46 months met the criteria, compared with only 2 of 10 aged <46 months. Social and affective abnormalities were most frequent; restricted interests and repetitive behaviors were largely absent. Lack of cognitive growth paralleled ADOS score.

Conclusion An increased incidence of ASD-like social behaviors was seen at age 3-4 years in children with early-onset MPS IIIA. Although more frequent in the severely impaired children, ASD-like behaviors were observed across the entire range of cognitive impairment. Clinicians must be aware that when a child acquires ASD-like behaviors, MPS IIIA should be included in the differential diagnosis. *(J Pediatr 2014;164:1147-51)*.

Mucopolysaccharidosis type IIIA (MPS IIIA) is a lysosomal disorder associated with progressive dementia and severe behavioral disruption. It is a rare (approximately 1 in 100 000 births)[1-4] autosomal recessive disease caused by decreased heparan-N-sulfatase (sulfamidase) catalytic activity, a necessary metabolic step in degradation of the glycosaminoglycan heparan sulfate. Undegraded heparan sulfate is evident in many cells of the central nervous system. Although MPS IIIA is a somewhat heterogeneous disorder, it is characterized by progressive neurodegeneration, dementia, and physical disability, with death typically occurring in the second decade of life.[5] In the classic form of MPS IIIA, symptoms become apparent between 2 and 6 years of age, although diagnosis often lags behind the appearance of the earliest symptoms.[6] Some patients with onset and diagnosis of MPS IIIA after age 6 years have a slower decline.[5,7]

Clinical observations and parent reports indicate that many children with MPS IIIA have behaviors commonly associated with autism spectrum disorder (ASD),[5,8,9] a pervasive developmental disorder characterized by impaired social communication, restricted interests, and repetitive behaviors. Declines in social connectivity and functional communication have been described in MPS IIIA, but not directly measured.[5,9,10] Restricted interests, behavioral rigidity, and repetitive behaviors have not been reported. A group of children with MPS IIIA was evaluated for ASD behaviors using a standard assessment method, the Autism Diagnostic Observation Schedule (ADOS),[11] in an effort to explore the behavioral evolution of the disease and provide guidelines for identification and intervention.

We hypothesized that those children with MPS IIIA who meet the ADOS criteria for ASD or autism will be older and consequently at a more advanced stage of disease compared with those who do not. In addition, we hypothesized that poor eye contact, social reciprocity, and communication skills, rather than rigid and repetitive interests and behaviors, will characterize children with MPS IIIA.

Methods

A total of 30 children with MPS IIIA were enrolled. Twenty-five children with MPS IIIA, age 2-18 years, were recruited into this neurobehavioral study from

ADOS	Autism Diagnostic Observation Schedule
ASD	Autism spectrum disorder
MPS IIIA	Mucopolysaccharidosis type IIIA

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a natural history study. Patients in the natural history study met the following criteria: (1) confirmed diagnosis of MPS IIIA by enzyme or mutation analysis; (2) minimum chronological age of 1 year; and (3) developmental age of at least 12 months on the Vineland Adaptive Behavior Scales.[12] We also enrolled 5 patients with MPS IIIA who were seen clinically and who met the same criteria but were not part of the natural history study.

The University of Minnesota's Institutional Review Board approved this neurobehavioral study as well as the longitudinal natural history study. Written informed consent was obtained from the parents or guardians of the children who served as subjects of the investigation.

Children in the study were classified as having either the classic, early form of MPS IIIA if diagnosed before age 6 years or the late-onset form with slower decline if diagnosed after age 6 years.[3,5] We found that diagnosis before age 6 was associated with severe genotypes, and that those diagnosed later had at least 1 mutation associated with late-onset MPS IIIA.[13] One child diagnosed with Sanfilippo syndrome after age 6 had been diagnosed with autism until a decline was noted; he had a known severe genotype and was retained in this sample.

To increase homogeneity and to use only 1 ADOS module, we excluded the 6 slowly progressing, late-diagnosed children from this neurobehavioral study, as well as 1 of their siblings, yielding a final sample of 23 children. One child who was diagnosed before age 6 had phrase speech and thus was given ADOS module 2, and 1 child was not given the ADOS. The final number for analysis was 21.

The ADOS is a semistructured observation tool designed to observe and judge the quality of a child's social communication and play and to assess for the presence of any intense interests or repetitive behaviors. The ADOS yields total scores for social affect and restricted and repetitive behavior, yielding an overall classification indicating behaviors and symptoms consistent with autism, consistent with milder indications of ASD, or not consistent with ASD ("nonspectrum"). To most effectively evaluate behaviors compatible with ASD using this measure, a cognitive age equivalent of at least 18 months is recommended. The ADOS comprises 4 different modules, with the tasks in each module tailored to the child's language level: (1) children who are nonverbal or who communicate in primarily single words; (2) children who regularly use phrase speech; (3) children who speak in full and complex sentences; and (4) older adolescents and adults with fluent language. In the current sample, we included only children who were administered module 1. We used the revised ADOS algorithms.[14]

Along with comparing total scores in the areas of social affect and restricted/repetitive behaviors, we also analyzed individual behaviors that are observed and coded on the ADOS. The 2 examiners who administered the ADOS were "research-reliable," a credential that indicates a high level of interrater reliability in coding.

The natural history study included a comprehensive evaluation of neurodevelopment using the Bayley Scales of Infant Development–Third Edition,[15] and those data are included in this neurobehavioral study. The Bayley Scales of Infant Development–Third Edition also was administered to clinical patients, by 2 experienced examiners. Only cognitive age-equivalents are reported here, because many of the patients were past the age at which standardized scores can be calculated.

Results

The sample of 21 children included 14 boys and 7 girls, with a mean age of 54 months (range, 22-106 months). Thirteen of the 21 children (62%) met the criteria for ASD using ADOS module 1. Table I presents patient characteristics. In this sample, the average age at diagnosis of MPS IIIA was 46 ± 19 months (range, 21-98 months); of note, this average does not include the siblings diagnosed because of the proband's diagnosis. Because the sample included 5 pairs of siblings, the average age is based on 16 diagnoses.

Table I. Patient characteristics

Characteristic	Total (n = 21)	ADOS non-ASD (n = 8)	ADOS ASD (n = 13)	Cognitive age equivalent <18 mo (n = 8)	Cognitive age equivalent >18 mo (n = 13)
Females, n (%)	7 (33.3)	2 (25.0)	5 (38.5)	2 (25.0)	5 (38.5)
Males, n (%)	14 (66.7)	6 (75.0)	8 (61.5)	6 (75.0)	8 (61.5)
Age, mo, mean (SD), range	54.1 (24.6), 22-106	33.5 (7.7), 22-45	66.8 (22.6), 26-105	42.8 (15.5), 26-105	72.6 (26.1), 22-76
Cognitive age equivalent, mo, mean (SD), range	19.5 (6.5), 8-27	24.1 (3.3), 21-30	16.6 (6.3), 8-27	12.5 (3.3), 8-17	23.8 (3.3), 19-30
Developmental quotient, mean (SD), range	46.5 (27.2), 8-91	74.1 (12.1), 55-91	29.5 (18.2), 8-62	22.6 (17.9), 8-62	61.2 (20.9), 26-91
Module 1, no words, n (%)	10 (47.6)	2 (25.0)	8 (61.5)	8 (100)	4 (31)
Module 1, some words, n (%)	11 (52.4)	6 (75.0)	5 (38.5)	0 (0.0)	9 (69)
Meets ADOS criteria for autism, n (%)	12 (57.1)	0 (0.0)	12 (92.3)	7 (87.5)	5 (38.5)
Meets ADOS criteria for ASD, n (%)	1 (4.8)	0 (0.0)	1 (7.7)	1 (12.5)	0 (0.0)
ADOS nonspectrum, n (%)	8 (38.1)	8 (100)	0 (0.0)	0 (0.0)	8 (61.5)
SA, mean (SD), range	10.5 (7.0), 0-20	2.5 (1.5), 0-5	15.5 (3.2), 10-20	16.00 (2.6), 12-19	7.15 (6.7), 0-20
RRB, mean (SD), range	2.2 (1.6), 0-6	0.9 (0.6), 0-2	3.0 (1.4), 1-6	3.25 (1.0), 2-5	1.54 (1.5), 0-6
Total SA + RRB, mean (SD), range	12.7 (8.1), 0-22	3.2 (2.1), 0-7	18.5 (3.3), 12-22	19.25 (2.31), 15-22	8.62 (7.7), 0-22

RRB, restrictive and repetitive behavior; *SA*, social affect.