Observational Prospective Natural History of Patients with Sanfilippo Syndrome Type B

Chester B. Whitley, PhD, MD[1], Maureen Cleary, MD[2], Karl Eugen Mengel, MD[3], Paul Harmatz, MD[4], Elsa Shapiro, PhD[5,6], Igor Nestrasil, MD, PhD[6], Patrick Haslett, MBBS[7], David Whiteman, MD[7], and David Alexanderian, DO[7]

Objective To evaluate the natural course of disease progression in patients with Sanfilippo syndrome type B (mucopolysaccharidosis type IIIB), identify potential end points for future therapy trials, and characterize biomarkers related to the disease.

Study design A prospective, multicenter study was conducted. Baseline, 6-month, and 12-month assessments included neurodevelopmental status (Bayley Scales of Infant Development, Third edition), adaptive status (Vineland Adaptive Behavior Scales, Second Edition), volumetric brain magnetic resonance imaging, cerebrospinal fluid heparan sulfate, and urine glycosaminoglycan (GAG) measurements.

Results Nineteen patients aged 1.6-31.7 years were enrolled. Over 12 months, cognition, adaptive behavior, and cortical gray matter volume (GMV) declined in most patients. For patients diagnosed at <6 years, although there was no overall mean change over 12 months, there were 10%-48%, 3%-66%, and 1%-14% decreases in cognitive development quotient score, Vineland Adaptive Behavior Scales, Second Edition development quotient score, and cortical GMV in 8/12, 9/11, and 10/11 patients, respectively. Mean urine GAG and cerebrospinal fluid heparan sulfate levels were stable, but patients diagnosed at <6 years (n = 14) had higher levels than those ≥6 years at diagnosis (n = 4), which was likely associated with age as they also were generally younger.

Conclusions Cognition, adaptive behavior, and cortical GMV measures sensitively tracked deterioration in patients with mucopolysaccharidosis type IIIB aged ≤8.6 years. Biomarkers may have prognostic value, but their sensitivity to disease progression requires further investigation. These findings should help evaluate enzyme replacement and gene therapy agents for this rare, devastating, neurodegenerative disease. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT01509768.

Sanfilippo syndrome type B, or mucopolysaccharidosis (MPS) type IIIB (MPS IIIB), is 1 of 7 MPS types;[1] there are 4 genetically distinct MPS type III subtypes (ie, A, B, C, and D). MPS IIIB, affecting approximately 1 in 250 000 live births,[2-6] is caused by a mutation in both copies of the alpha-N-acetylglucosaminidase gene (*NAGLU*), located on chromosome 17q21.1. The most dramatic clinical manifestations of MPS IIIB are neurologic. More than 120 *NAGLU* mutations have been described, mostly missense mutations, but nonsense mutations, deletions, insertions, and splice-site mutations also exist.[7,8] This wide allelic heterogeneity presents challenges in identifying genotype-phenotype correlations.[6,9] Patients with an attenuated phenotype carry at least 1 mild missense mutation, allowing for residual *NAGLU* activity.[10]

Typically manifesting at 1-4 years of age,[6] the most prominent progressive symptoms of MPS IIIB are neurologic. Children appear normal at birth and throughout infancy, and progressive brain injury may initially be misdiagnosed as autism. Only as a child reaches preschool or school age do the symptoms of this debilitating disease become apparent. Lacking treatment, affected children slowly progress through 4 phases from developmental delays, surviving into the second or third decade of life. In its severest form, MPS IIIB culminates in dementia and death by the late teens.[6,11] A group of patients in The Netherlands with attenuated MPS IIIB had a slow progression of signs that occasionally included nonspecific psychiatric manifestations and

BSID-III	Bayley Scales of Infant Development, Third Edition
CHQ-PF50	Child Health Questionnaire Parent Form, 50 items
CSF	Cerebrospinal fluid
DQ	Development quotient
GAG	Glycosaminoglycan
GMV	Gray matter volume
KABC-II	Kaufman Assessment Battery for Children, Second Edition
ITQOL	Infant Toddler Quality of Life
MPS	Mucopolysaccharidosis
MPS IIIB	Mucopolysaccharidosis type IIIB
MRI	Magnetic resonance imaging
NAGLU	alpha-N-acetylglucosaminidase gene
VABS-II	Vineland Adaptive Behavior Scales, Second Edition

From the [1]Gene Therapy Center, University of Minnesota, Minneapolis, MN; [2]Great Ormond Street Hospital, London, United Kingdom; [3]Villa Metabolica, Center for Pediatric and Adolescent Medicine, MC University of Mainz, Mainz, Germany; [4]UCSF Benioff Children's Hospital Oakland, Oakland, CA; [5]Shapiro Neuropsychology Consulting LLC, Portland, OR; [6]Department of Pediatrics, University of Minnesota, Minneapolis, MN; and [7]Shire, Lexington, MA

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were diagnosed in adulthood.[12] A study of patients with MPS IIIA and IIIB in France, Greece, and the United Kingdom found a comparable disease in affected individuals, with similar patterns of delayed language acquisition and cognitive decline, as well as disruptive behavior, especially in those diagnosed before 5 years of age.[6]

Diagnosis is suspected by the detection of elevated levels of glycosaminoglycan (GAG) in urine.[13-15] Definitive laboratory confirmation of a suspected clinical phenotype depends on a comprehensive assessment of urine GAG substrate, deficient NAGLU enzyme activity, and the identification of pathologic mutations.[10,16] There is no proven effective therapy for MPS IIIB, but encouraging phase 1 results have been reported with enzyme replacement therapy[17] and gene therapy.[18] Management currently is symptomatic.[7] Toxic secondary metabolite accumulation, limited neuronal survival, and neuroinflammatory sequelae, resulting in the loss of cortical gray matter and cognitive skills, are thought to contribute to MPS IIIB pathophysiology.

This study was undertaken to better understand the clinical spectrum and progression rate of MPS IIIB and, therefore, to enable the identification of patient subpopulations characterized by disease stage and phenotype who may benefit from future interventional clinical studies. As with MPS IIIA,[19] a paramount functional manifestation of MPS IIIB is cognitive decline. This study hypothesized that well-standardized measures of development quotient (DQ) and cortical gray matter volume (GMV) could serve as appropriate clinical end points. Clinical, neuroimaging, and biochemical tests were explored to identify potential surrogate end points for future trials.

Methods

This MPS IIIB natural history study, initiated in April 2012, was a multicenter, longitudinal, prospective study (ClinicalTrials.gov: NCT01509768). The study was conducted in compliance with the US Food and Drug Administration, Institutional Review Board regulations in 21 Code of Federal Regulations 56, and the International Conference on Harmonisation Good Clinical Practice guidelines. Written consent and/or assent were provided by the patient or the patient's parent or legal guardian before any study-related procedures were initiated. The study was conducted according to ethical principles of the Declaration of Helsinki, consistent with International Conference on Harmonisation Good Clinical Practice guidelines and applicable regulatory requirements, including 21 CFR Parts 50, 54, 56, and 312.

Medically stable patients who were ≥1 year of age with 2 *NAGLU* mutations at screening or an enzyme deficiency of ≤10% of the lower limit of the testing laboratory's normal range were enrolled. An upper age limit of 10 years was implemented in March 2013 as an amendment to the study protocol to focus on the younger, childhood age group. The inclusion criteria also required patients to have an age equivalence of ≥1 year as assessed by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II),[20] a parent-reported observational measure. The key exclusion criteria were significant non-MPS IIIB-related central nervous system impairment or behavioral disruption, visual or hearing impairment to a level that could impede neurodevelopmental testing, bleeding disorders, the inability to undergo anesthesia or control seizures, or a history of hematopoietic stem cell or bone marrow transplantation.

Patients were screened within 30 days before study initiation and details of the genotypic mutation, sex, race, age at enrollment (chronological age), age at diagnosis, and head circumference were recorded. Sibling information was not collected in the study. The study had a planned sample size of 25 patients, assuming a 20% dropout rate to assess longitudinal data adequately. Clinical, developmental, imaging, and biochemical assessments were performed over a 4-day period at study initiation (baseline) and then again at 6 months (±14 days) and 12 months (±14 days) poststudy initiation.

Study End Points

Planned standardized tools for the assessment of the neurodevelopmental status and adaptive status of patients were the Bayley Scales of Infant Development, Third Edition (BSID-III), the Kaufman Assessment Battery for Children, Second Edition (KABC-II), and VABS-II.[20-22] The BSID-III measure evaluates the cognitive, motor, and language cognitive development of infants and toddlers aged 0-42 months. In severely impaired children, DQ (the ratio of age-equivalent score to chronological age) is the accepted metric to avoid the "floor" effect of standardized scores.[19,23] The KABC-II Nonverbal Ability Scale is a cognitive assessment for patients with normative data aged 3-18 years; as patients were either too young or their level of developmental impairment was too severe, no patients were evaluated using the KABC-II measure. The parent-observational report, VABS-II, consists of 5 key domains of communication, daily living skills, socialization, motor skills, and the adaptive behavior composite.[20] The average VABS-II age-equivalent composite score, calculated without the motor component, has been shown to be strongly associated with the cognitive measures.[23] For that reason, the motor skills component was excluded in the calculation of the composite score in this study.

Health-related quality of life was measured using the Child Health Questionnaire Parent Form, 50 items (CHQ-PF50) and the Infant Toddler Quality of Life (ITQOL), either of which was administered according to the patient's developmental age (age-equivalent score). The CHQ-PF50, encompassing 13 health concepts, was designed for patients aged 5-18 years to measure the physical and psychosocial well-being of children and parents or caregivers of affected children.[24] The ITQOL measures similar concepts for children who are 2 months to 5 years of age.[25] However, ITQOL and CHQ-PF50 data at baseline, 6 months, and 12 months were missing for a large number of patients and are, therefore, not described.

Imaging analyses included serial brain magnetic resonance imaging (MRI) studies followed by automated volumetric analysis.[19,26] MRI quantitative analyses for all patients in the study were performed at the University of Minnesota (the central reader for MRI data). Automated volumetric

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