Longitudinal Natural History of Pediatric Subjects Affected with Mucopolysaccharidosis IIIB

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Objective To characterize the longitudinal natural history of disease progression in pediatric subjects affected with mucopolysaccharidosis (MPS) IIIB.

Study design Sixty-five children with a confirmed diagnosis of MPS IIIB were enrolled into 1 of 2 natural history studies and followed for up to 4 years. Cognitive and adaptive behavior functions were analyzed in all subjects, and volumetric magnetic resonance imaging analysis of liver, spleen, and brain, as well as levels of heparan sulfate (HS) and heparan sulfate nonreducing ends (HS-NRE), were measured in a subset of subjects.

Results The majority of subjects with MPS IIIB achieved an apex on both cognition and adaptive behavior age equivalent scales between age 3 and 6 years. Development quotients for both cognition and adaptive behavior follow a linear trajectory by which subjects reach a nadir with a score <25 for an age equivalent of 24 months by age 8 years on average and by 13.5 years at the latest. All tested subjects (n = 22) had HS and HS-NRE levels above the normal range in cerebrospinal fluid and plasma, along with signs of hepatomegaly. Subjects lost an average of 26 mL of brain volume (−2.7%) over 48 weeks, owing entirely to a loss of cortical gray matter (32 mL; −6.5%).

Conclusions MPS IIIB exists along a continuum based on cognitive decline and cortical gray matter atrophy. Although a few individuals with MPS IIIB have an attenuated phenotype, the majority follow predicted trajectories for both cognition and adaptive behavior. *(J Pediatr 2022;249:50-8)*.

Trial registration ClinicalTrials.gov identifiers NCT02493998, NCT03227042, and NCT02754076.

Mucopolysaccharidosis (MPD) type III (or Sanfilippo syndrome; OMIM #252920) is a group of lysosomal storage diseases caused by autosomal recessive defects in 1 of the 4 enzymes involved in the degradation of heparan sulfate (HS) (MPS IIIA-D). MPS IIIB is caused by deficiency in alpha-N-acetylglucosaminidase (NAGLU) enzyme activity. Recent publications have reported a specific MPS IIIB prevalence of 0.21 cases in 100 000 births worldwide.[1] In the US, 40 subjects diagnosed with MPS IIIB joined the MPS Society between 1995 and 2015.[2]

In contrast to other MPS disorders, subjects with MPS IIIB have a predominantly neurodegenerative phenotype with few peripheral manifestations. Affected children initially present with developmental delay between the age 1 and 4 years.[3] As the disease progresses, it is characterized by severe hyperactivity,

BSA	Body surface area
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CSF	Cerebrospinal fluid
DQ	Developmental quotient
HS	Heparan sulfate
HS-NRE	Heparan sulfate non-reducing ends
KABC-II	Kaufman Assessment Battery for Children, Second Edition
MPS	Mucopolysaccharidosis
MRI	Magnetic resonance imaging
NAGLU	Alpha-N-acetylglucosaminidase
VABS-II	Vineland Adaptive Behavior Scales, Second Edition

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sleep-wake disturbance, loss of impulse control, severe behavioral disturbances, and intellectual decline. Behavioral symptoms wane with the onset of severe dementia and decline of all motor functions, resulting in complete loss of locomotion and bulbar dysfunction.[4] A UK study estimated the life expectancy of individuals with MPS IIIB as 19 ± 7 years, with respiratory tract infections the leading cause of death.[5] A distinct subset of individuals with attenuated MPS IIIB has been described with residual NAGLU activity and a median life expectancy of 43.5 years.[6,7]

Although MPS IIIA disease progression has been well described,[8-10] much less longitudinal and population data have been published for MPS IIIB.[9,11] Our studies were designed to expand on the scarce published longitudinal data describing the natural history of MPS IIIB in young subjects and to provide a solid basis for interpreting results of future treatment studies.

Methods

Study Designs

To enroll a representative global MPS IIIB population for these 2 prospective, multicenter, multinational, longitudinal natural history studies, subjects were recruited from 10 centers around the globe. All study participants had deficient NAGLU enzyme activity confirmed by genetic testing and enzyme activity and presented with signs/symptoms consistent with the disease. The first study (NCT02493998; study 250-901 hereinafter) enrolled 22 subjects with MPS IIIB age >1 and <11 years with an adaptive behavior age equivalent score ≥12 months as assessed by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[12] and a cognitive developmental quotient (DQ) ≥50 as assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)[13] or the Kaufman Assessment Battery for Children, Second Edition (KABC-II).[14] Subjects were followed for up to 72 weeks; those who completed at least 48 weeks were eligible to enroll in treatment study 250-201 (NCT02754076). When available, any additional pretreatment values for study 250-201 were included in the current analysis.

The second study (NCT03227042; study 250-902 hereinafter) fully enrolled 43 subjects with MPS IIIB aged 0-18 years; there was no minimum requirement for adaptive behavior or cognitive scores. The study duration was 4 years, or 192 weeks. A year was defined as 48 weeks for ease of study design. At the time of this publication, a few subjects have completed the study; study should be completed by 2024.

The key exclusion criteria were non-MPS IIIB cognitive decline, participation in another natural history study, and receipt of or scheduled receipt of any investigational medication for MPS IIIB or other disorders. Key exclusion criteria for study 250-901 included any contraindication for neurosurgery or magnetic resonance imaging (MRI), a history of poorly controlled seizure disorder, potential complications from intracerebroventricular drug administration, and the need for ventilation support at night.

The study protocols were reviewed and approved by the competent authorities in each country, as well as the site-specific Ethics Committee/Institutional Review Board. Written informed consent from a parent or legal guardian and assent from the subject, if applicable, were obtained before specific assessments were performed.

Cognition

Cognitive function was measured using validated and standardized measures of cognition, the nonverbal scales of the BSID-III or the KABC-II. The choice of test was determined at study screening and for further visits using a predefined algorithm (**Appendix**; available at www.jpeds.com). Age-equivalent scores from published normative data were obtained from raw scores, and the DQ was derived by dividing the age equivalent by chronological age and then multiplying by 100. The use of age equivalent scores circumvents the "floor effect" of standardized scores when applied to children with severe cognitive impairment.[15] Raw scores (ie, numbers of correct responses) allow the generation of an age equivalent score and a DQ; these latter scores for the cognitive domain are presented hereinafter. Mean raw scores also were analyzed, but data are not presented here. Mean age equivalent scores for the nonverbal index were averaged over the administered domains and are presented hereinafter.

Adaptive Behavior

Adaptive behavior was measured by parent report using the VABS-II[12]; age equivalent scores and DQ were generated as was done for cognitive testing. The VABS-II is a validated and standardized measure of adaptive behavior administered to caregivers by a qualified rater. The resulting item scores for each subtest are then converted into age equivalent scores; mean age equivalent scores were calculated for each domain and for the total score without the motor domain. Age equivalent scores were converted into DQ by dividing the age equivalent by chronological age and then multiplying by 100.

MRI

Head and abdominal MRI was used to assess regional liver, spleen, and brain volumes at baseline, week 24, and week 48 of study 250-901. Volumetric analysis was performed on 3-dimensional T1-weighted MRI using FreeSurfer Image Analysis Suite version 5.3 (Martinos Center, Harvard University),[16] as described previously.[11,17] This analysis yielded surface-based cortical parcellation and volume-based morphometric segmentation.

Liver and spleen volumes were calculated by ICON. Because liver and spleen volumes increase linearly compared with both age and body surface area (BSA), these volumes

were normalized to BSA calculated using the Mosteller formula.[18] Normal ranges for BSA-corrected liver and spleen volumes were estimated based on the literature.[19,20]

Brain volumes were expressed without normalization, similar to previous publications.[11,21] Brain volume ranges of 4- to 9-year-old nonaffected subjects are given in Table I (available at www.jpeds.com) for reference.[22]

Laboratory Testing

In study 250-901, HS and HS nonreducing end (HS-NRE) measurements were performed by ARUP Laboratories on cerebrospinal fluid (CSF) and plasma specimens using a previously described method.[23] *NAGLU* genotyping and enzyme activity testing were performed by Greenwood Genetic Center.

Historical Data

Adaptive scores, brain MRI, and corresponding ages from Whitley et al[11] and Truxal et al[9] were approximated using DigitizeIt (https://www.digitizeit.xyz/).[24] Cognitive data were approximated using the same approach and derived from the same publications.[25]

Statistical Analysis

Two-tailed paired and unpaired *t*-tests and linear and nonlinear correlation analyses were performed using Prism 9.3.1 (GraphPad Software).

Results

Subjects

A total of 65 subjects were enrolled in the 2 studies. Baseline clinical characteristics are presented in Table II (available at www.jpeds.com). Based on previous literature related to MPS III, diagnosis above 6 years of age has been a marker for milder disease.[11,26] Sixty-one subjects were diagnosed between age 3 months and 77 months, and 4 subjects were diagnosed at age 91-156 months. The average age at diagnosis was 36 months (median, 35 months); females were diagnosed later than males (mean, 41 months vs 30 months; median, 39 months vs 25 months; $P = .04$). Fifty-six genetic variants were observed among the subjects, 30 of which are unique allelic variants that have not been described previously; none of the 4 subjects diagnosed after age 6 years were homozygous for their *NAGLU* allelic variants (Table III). Three of the subjects diagnosed after age 6 years were found to carry *NAGLU* allelic variants associated with an attenuated disease phenotype,[6,27] and were not incorporated into the overall analyses. Because the fourth subject diagnosed after age 6 years did not have a known *NAGLU* genotype associated with attenuated disease and had an age equivalent score of 48 months at age 115 months, the subject was not classified as attenuated.

Table III. Summary of subjects' *NAGLU* allelic variants

NAGLU allelic variants	Age ≤6 y at diagnosis (N = 61)	Age >6 y at diagnosis (N = 4)
Homozygous subjects, n (%)	34 (56)	0 (0)
Allelic variants observed, n	52	6
Subjects with unique allelic variants, n (%)	28 (46)	2 (50)
Most common allelic variants, n		
p.R565W	5	2
p.Y140C	4	0
p.R234C	4	0
c.1022-2A>G	4	0
p.R297ter	3	0
p.A72_G79dup	3	0
p.F245L	3	0
p.D312N	3	0
p.Y65Tfs*57	3	0
p.R565Q	2	1
p.S612G*	0	2
p.H227P*	0	1
p.Q176ter	0	1
p.R565G	0	1

*Allelic variants known to be associated with attenuated MPS IIIB disease phenotype.

Cognitive and Adaptive Behavior Trajectories

Cognitive age equivalent or DQ scores and adaptive behavior scores were plotted against chronological age for all subjects of both natural history studies (Figure 1, A-D). Approximated data from previously published natural history studies were included in analyses of age equivalent and DQ scores for comparison.[9,11,25] Three subjects carrying *NAGLU* allelic variants associated with an attenuated phenotype had both cognitive and adaptive behavior age equivalent scores >72 beyond age 84 months. Except for these three attenuated subjects, most subjects reached a cognitive and adaptive behavior apex between age 36 and 72 months (3-6 years). Past age 11 years (132 months), the maximal observed age equivalent score was 31 months for cognition (Figure 1, A) and 46 months for adaptive behavior (Figure 1, C). As has been reported previously,[15,28] significant correlation exists between cognitive and adaptive behavior age equivalent scores ($r = 0.69$; $P < .0001$).

Baseline cognitive and adaptive behavior DQ scores showed a negative linear relationship with chronological age (Figure 1, B, D). These linear regression analyses demonstrated that subjects with nonattenuated MPS IIIB reached a cognitive and adaptive behavior nadir of DQ = 25 by age 8 years (96 months) on average and by 13.5 years (162 months) at the latest.

To better understand the rates of cognitive and adaptive behavior decline in children with MPS IIIB without an attenuated phenotype, individual DQ slopes were calculated using the following formula: (DQ score at week 48 – DQ score at baseline)/(age at week 48 – age at baseline). This formula estimated a rate of monthly decline for each subject with available data (ie, 43 subjects for cognition and 48 for adaptive behavior) within 1 year of observation from the time of enrollment (48 weeks). Between the baseline ages of 12 and

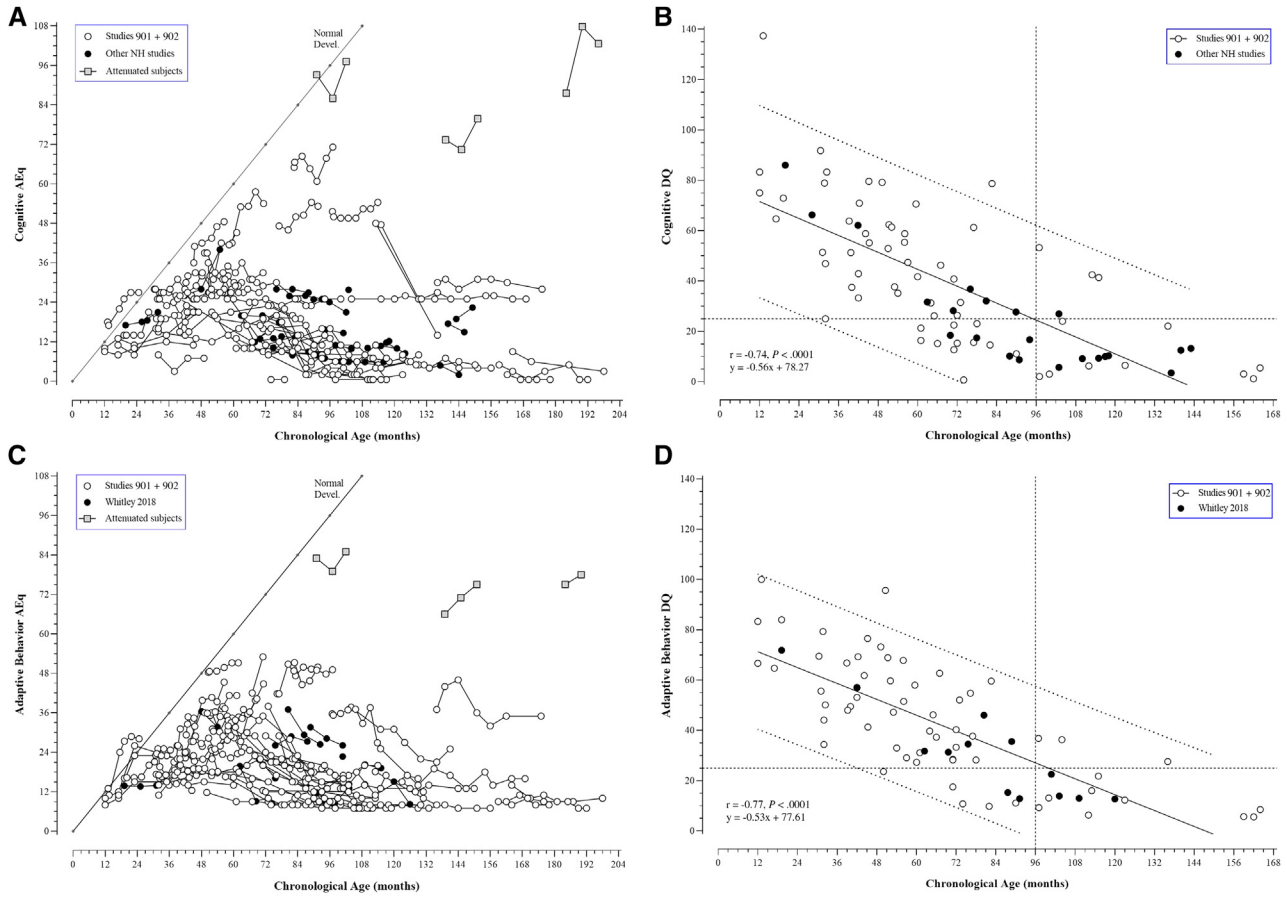


Figure 1. **A,** Changes in cognitive age equivalent score over chronological age shown for subjects in studies 250-901 and 250-902 (data available as of November 2021; *open circles*). The 3 subjects with attenuated phenotype from study 250-902 are denoted by gray boxes. Previously published data (digitized as described in Methods) are shown as black dots.[9,11,25] **B,** Regression analysis of cognitive DQ score at baseline vs chronological age for subjects in studies 250-901 and 250-902 as well as subjects from previously published studies,[9,11,25] with attenuated subjects excluded. Cognitive DQ follows a linear decline ($y = -0.56x + 78.27$; $r = -0.74$; $P < .0001$). **C,** Changes in adaptive behavior age equivalent score, as assessed using the VABS-II instrument,[16] over chronological age for subjects in studies 250-901 and 250-902 (data available as of November 2021, shown as open circles). Three subjects with attenuated MPS IIIB are denoted by gray boxes. Previously published data (digitized as described in Methods) are shown as black dots.[9,11] **D,** Regression analysis looking at adaptive behavior DQ score at baseline vs chronological age for subjects in **C,** excluding the attenuated subjects. Adaptive behavior DQ follows a linear decline ($y = -0.53x + 77.61$; $r = -0.77$; $P < .0001$). *AEq*, age equivalent; *NH*, natural history.

60 months (1-5 years), the rates of change in cognition and adaptive behavior varied greatly among the subjects with MPS IIIB (range, −4.0 to +3.0). Over time, the variability in the rates of change of these measures narrowed, and beyond age 8 years (96 months), the rates of change in cognitive and adaptive behavior DQ score varied only between +0.5 and −0.5. A reduction in cognitive DQ slope vs chronological age is defined by a trajectory that follows a second-degree polynomial equation ($R^2 = 0.43$) (**Figure 2**). No clear trajectory could be defined for adaptive behavior.

HS

In the absence of NAGLU enzyme activity, undegraded HS-NRE accumulates in fluids and tissues. HS and HS-NRE levels were elevated in plasma and CSF of all subjects (n = 22 in study 250-901) at all time points measured (**Table IV**; available at www.jpeds.com). Levels were relatively stable for any given subject over time, and the mean and median HS and HS-NRE concentrations also were similar over time. Very strong correlations between total HS and HS-NRE levels in CSF and plasma were observed at all 3 time points (**Table IV**).

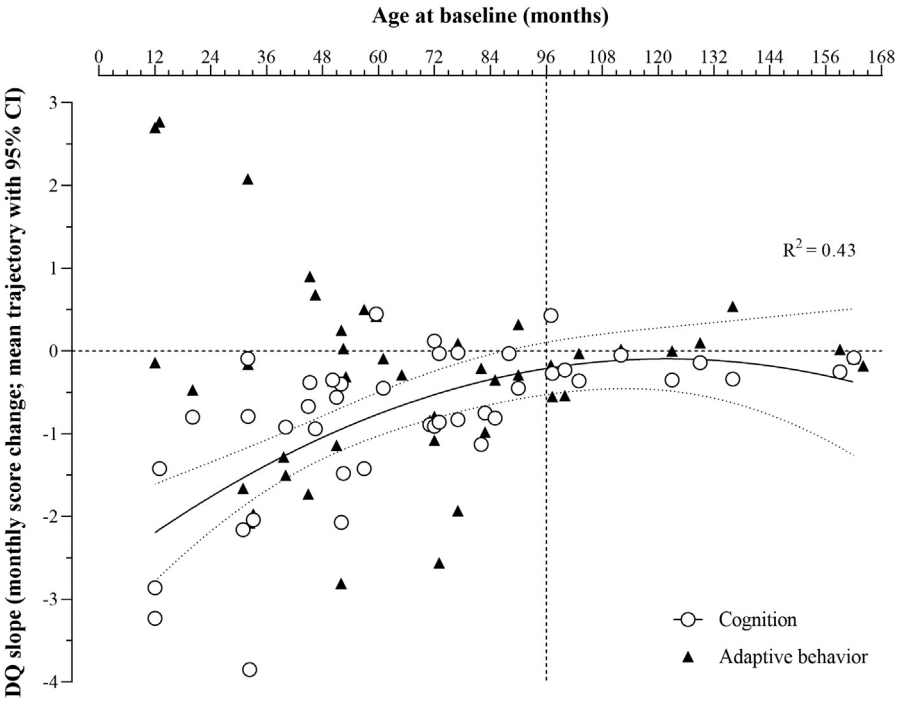


Figure 2. Slopes of cognitive (open circles) and adaptive behavior (black triangles) DQ vs age at baseline. DQ slopes were calculated using the formula (DQ at week 48 – DQ at baseline)/(age at week 48 in months – age at baseline in months) for subjects in both natural studies for whom both values were available (n = 43 and 48 for cognition and adaptive behavior, respectively). The correlation between cognitive DQ slope and age at baseline (R^2 = 0.43) was established using a second-order polynomial equation. No significant correlation was observed between age and VABS-II DQ slope.

Hepatomegaly and Splenomegaly in Subjects with MPS IIIB

All assessed subjects had hepatomegaly at baseline with BSA-corrected liver volume above the normal range for children aged 2-9.5 years, and their liver volume increased slightly but significantly from baseline to week 48 (Table I). BSA-corrected liver volume was correlated with plasma HS-NRE level (r = 0.67; P = .001 at study 250-901 baseline), but not with CSF HS-NRE level. Despite this hepatomegaly, no subjects had clinical or biochemical evidence of hepatic dysfunction. Pain, discomfort, or limitations in mobility owing to hepatomegaly were not assessed. Splenomegaly was observed in some subjects, and spleen volume remained stable over the 48-week study (Table I).

Subjects with MPS IIIB Lost Cortical Gray Matter over Time

Volumetric measurements of brain regions are presented in Table I. Brain atrophy (ie, −26 mL on average) in subjects with MPS IIIB appeared to be driven primarily by a loss of cortical gray matter (ie, −32 mL on average), because subjects lost volume in this region over the 48-week study period but did not display a similar decrease in other brain regions. Cerebellum was not affected by disease progression, at least based on MRI data, and even increased in volume as would be expected of 2- to 10-year-old children, although ventricular volume increased significantly over the course of the study (Table I).

We combined our data with data from subjects diagnosed before age 6 years as described previously[11] and evaluated the dynamics of cortical gray matter loss over time. Subjects with MPS IIIB aged <24 months generally have cortical gray matter volume within the normal range (Figure 3). Subjects aged >24 months displayed a loss of cortical gray matter volume over the study period; beyond age 8 years, subjects had cortical gray matter volume below the normal range (Figure 3).

Discussion

Here we report the results of 2 natural history studies with a total of 65 subjects with MPS IIIB enrolled across 10 clinical sites worldwide. The subjects were followed for at least 48 weeks and up to 4 years in some cases. Their data provide a comprehensive picture of MPS IIIB in terms of age at diagnosis, *NAGLU* genotyping, concentrations of HS and HS-NRE in CSF and plasma, and changes in volumes of liver, spleen, and brain regions over time. Together with previously published data, our findings establish that the majority of subjects with MPS IIIB, excluding those with an attenuated phenotype, reach a cognition and adaptive behavior nadir by age 8 years

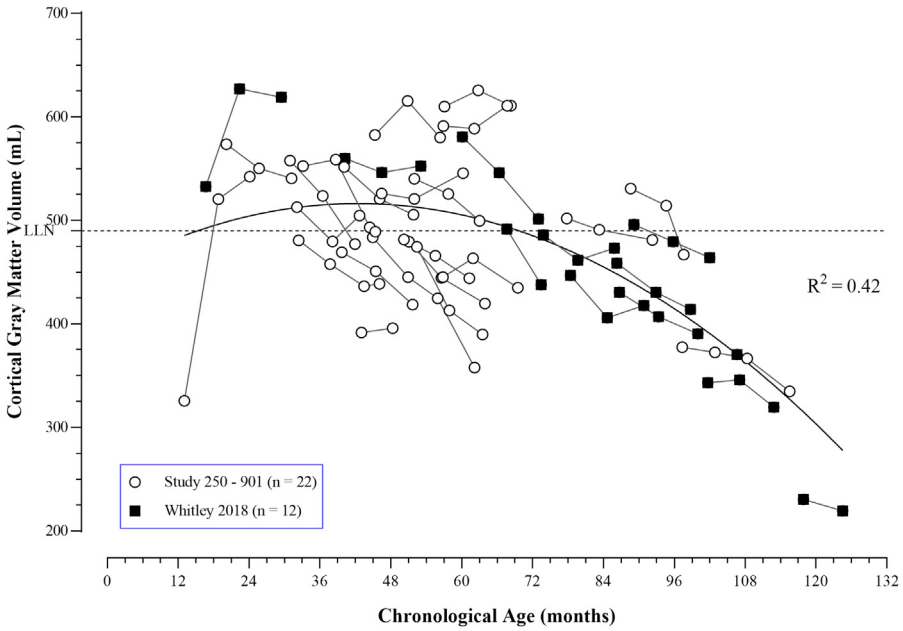


Figure 3. Changes in cortical gray matter volume over chronological age for subjects in study 250-901 (*open circles*). Previously published data (estimated via DigitizeIt as described in Methods) from subjects diagnosed before age 6 years were included (black squares).[24] Each line represents an individual subject (n = 34) whose samples were tested every 6 months. The lower limit of normal cortical gray matter volume (489 mL; *gray dashed line*), was established by evaluating brain MRI data in 17 nonaffected boys and 18 girls aged 4-8 years (48-96 months). Within this age window, some brain volumes might increase slightly over chronological age; however, variability was greater among subjects of similar age.[22] Cortical gray matter volume decreased over time following a second-order polynomial equation (R^2 = 0.42 with all values included and R^2 = 0.54 with only baseline values considered). By age 10 years (120 months), no subject with nonattenuated MPS IIIB in these studies had cortical gray matter volume within the normal range.

(96 months) on average and by 13.5 years at the latest independent of their age of onset. Although some nonattenuated subjects had unchanged cognitive age equivalent scores over the study period (**Figure 1**, A), their adaptive age equivalent scores (**Figure 1**, C) and cognitive and adaptive behavior DQ scores fell within the trajectories of the general nonattenuated population (**Figure 1**, B, D), supporting a single continuum of disease progression.

This single disease continuum distinguishes MPS IIIB from MPS IIIA; in the case of MPS IIIA, some "slow-progressing" nonattenuated subjects present with relatively preserved cortical gray matter volume between age 100 and 200 months, supporting the existence of a distinct MPS IIIA slow progressor population independent of the rapid progressors and attenuated subjects[26] (**Figure 2**). Diagnosis before age 6 years (72 months) has been used to distinguish rapid from slow progressing phenotypes for individuals with MPS III with neuronopathic manifestations.[8,29,30] A strict 6-year cutoff might not be easy to maintain, considering that 8 of our subjects were diagnosed between 68 and 77 months of age. No other variables, such as *NAGLU* genotype (**Table III**) or MRI volumetric measurements (**Table I**), are predictive of disease onset or severity of phenotype or support a distinction between slow and rapid progressors as has been described for individuals with MPS IIIA.[26]

The natural history of MPS IIIB disease is closer to what has been published for MPS II, where there are severe and attenuated patient populations.[31] MPS II is classified as a severe neuronopathic form with significant neurocognitive deficits and an attenuated form considered to have little to no neurocognitive consequences.[32,33] Similar to what we describe for MPS IIIB, individuals with severe MPS II present with initial symptoms between 2 and 4 years of age, although there is significant variability in their age of developmental arrest.[33,34]

Three subjects with MPS IIIB with attenuated disease were identified in our studies. All 3 subjects were reliably identified genetically with known attenuated *NAGLU* variants and with an age equivalent score >72 months at age 84 months. Attenuated subjects are also likely to have limited brain atrophy; however, these patients were not assessed by MRI in our studies.

Even though DQ and age equivalent measures have limitations, both may be useful for assessing cognitive decline in individuals with MPS IIIB. DQ might not be useful in older subjects in whom cognitive and adaptive functions are low but constant. Conversely, the age equivalent score amplifies cognitive and adaptive differences among children of very

young age. Children with MPS III vary in their cognitive resources and resilience as do typically developing children, and so a decline in age equivalent score may be less apparent in some children than in others early on. The use of raw scores has been suggested for subjects with higher functioning.[35] Raw scores seem to show a broader dynamic range and a better separation between children who are cognitively steady and children who are progressing early. For now, however, we do not see a clear advantage of using raw scores over age equivalent scores (data not shown), especially because total raw scores are not generated for subjects tested on the KABC-II instrument. Assessing the use of raw scores vs growth scale values merits further consideration in future clinical trials.

The cognitive and adaptive age equivalent and DQ scores illustrate variabilities in the occurrence of symptoms and rate of decline in early stages of MPS IIIB, before 8 years of age. Despite this diversity, all individuals with nonattenuated MPS IIIB reach a cognition and adaptive behavior nadir by 13.5 years (162 months) independent of their age of onset. Past age 8 years (96 months), the rates of disease progression (ie, DQ slopes) are more homogenous among individuals with MPS IIIB (**Figure 3**). Others have raised the concern that the heterogeneity of MPS III disease could make assessing drug efficacy in clinical trials difficult.[36] The age window of 8-10 years could provide a time frame in which to measure the clinical benefit of potential therapies when individuals with MPS IIIB are expected to reach an inexorable cognitive and adaptive behavior nadir. Prior to this period, the lack of correlation between *NAGLU* genotyping and disease severity and the broad distribution of DQ slopes make it difficult to separate effects of treatment from the natural course of the disease. Changes in rates of cognition and adaptive behavior loss as measured by changes in slope may be a powerful way to demonstrate treatment efficacy while correcting for baseline differences. Treatment should start as early as possible, but assessment of efficacy of a treatment on cognitive decline between age 8 and 10 years may be most appropriate.

The pathophysiological role of accumulated HS in MPS III is relatively well understood.[37] Correlations between plasma HS level and loss of either speech or walking have been described in individuals with MPS III.[38] All tested subjects with MPS IIIB had both HS and HS-NRE levels above normal range in both CSF and plasma. Levels of HS and HS-NRE were highly correlated in CSF and plasma suggesting that the two analytical assays are useful to detect the accumulated substrate in MPS IIIB. There was no correlation between plasma or CSF HS-NRE and either cognitive age equivalent or DQ, even within a narrowed age window of 2-6 years (24-72 months), in which a broader variability is observed among individuals with MPS IIIB in terms of cognition, adaptive behavior, and brain atrophy. There also was no correlation between either plasma or CSF HS and HS-NRE and cortical gray matter volume. HS and HS-NRE cannot be qualified as markers of disease severity or disease progression; however, accumulation of HS or HS-NRE is indicative of a disease process. Achieving HS normalization in both CSF and plasma should be a primary goal of therapeutic intervention, and sustained HS or HS-NRE normalization in these fluids over long periods is reasonably likely to be predictive of clinical benefits.

All the subjects assessed in our studies had evidence of hepatomegaly. An enlarged liver reflects an accumulation of HS in the hepatic tissue; hepatomegaly appears to be a common feature of children with MPS IIIB that can affect liver function, quality of life, appetite, mobility, and perhaps respiratory function. In MPS III, an abnormal activation of the innate immune system is part of the disease process.[39,40] The mildly enlarged spleen volumes observed in some subjects might reflect an underlying inflammatory process rather than an HS accumulation.

Cortical gray matter atrophy has been described previously in relation to cognitive decline and other disease manifestations in MPS III.[11,26] Our data are consistent, and expand in the case of MPS IIIB, the brain volume data reported in a recent publication.[21] In fact, the 32-mL decrease in cortical gray matter observed in our study over 48 weeks is in line with the yearly 42-mL decrease described by Abreu et al,[21] especially given the younger age range of the subjects in our studies. The stable cortical white matter and increased cerebellar volumes over the course of study 250-901 also are consistent with the data reported by Abreu et al.[21] In the future, cortical gray matter atrophy might be an unbiased means to separate attenuated subjects from subjects with more severe disease; one would predict that attenuated subjects have sufficient residual NAGLU enzyme activity to prevent massive HS accumulation, neuronal cell death, and loss of gray matter volume.

A major shortcoming of our studies is the fact that brain and abdominal MRI data were not collected and HS and HS-NRE levels were not assessed in CSF and plasma of the study 250-902 subjects. Collection of these data would have greatly enhanced our ability to accurately define brain volume trajectories and changes in liver and spleen volumes over the course of MPS IIIB disease progression, particularly in attenuated subjects. In addition, a more quantitative NAGLU enzymatic assay would have been useful in assessing the relationship between residual enzyme activity and HS or HS-NRE levels in CSF and plasma.

All individuals with nonattenuated MPS IIIB exist along a single disease continuum and have predictable progression and predefined trajectories in terms of cognition, adaptive behavior, and brain atrophy equivalent to individuals with severe MPS II[31] and rapid MPS IIIA.[26] Some children might show deviation from normal development by age 1 year and some by age 4 years; most individuals with MPS IIIB will reach a cognitive DQ score <25 by age 8 years, and all will do so by age 13.5 years at the latest. Only a small subpopulation of individuals with MPS IIIB is recognized as attenuated, based mainly on NAGLU genotyping, age equivalent score >72 months by age 84 months, and, for now, age at diagnosis. Establishing disease trajectories is essential to predicting

treatment efficacy despite MPS IIIB disease heterogeneity in the early disease phase. Quantifying either a deviation in the slopes of cognitive and adaptive behavior before subjects reaching their nadir or the respective proportions of treated vs natural history subjects who did not reach their nadir might be 2 options to demonstrate the efficacy of an experimental therapeutic modality in this population of patients with MPS IIIB. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Immunodeficiency and Autoimmunity—Are There Common Pathways?

McLaughlin JF, Schaller J, Wedgwood RJ. Arthritis and immunodeficiency. J Pediatr 1972;81:801-3.

The authors reported the development of joint manifestations in 35 patients from the University of Washington, with immunodeficiency. Of them, 25 patients had hypogammaglobulinemia. Previous reports observed "a baffling propensity" of polyarthritis in patients with agammaglobulinemia, indistinguishable from juvenile rheumatoid (idiopathic) arthritis. The authors found 6 patients with transient arthritis or arthralgia; only 1 patient had chronic polyarthritis. Even though the incidence of joint disease in this cohort was lower than previous reports, the authors concluded that there is a coexistence of chronic arthritis and immunodeficiency. Lacking the understanding of immune pathways we have today, it is interesting to see how this phenomenon raised questions concerning autoimmunity as being part of the pathogenesis of chronic arthritis. The authors concluded that the coexistence of arthritis and immunodeficiency reinforced the theory that an unidentified infectious agent was the cause of the development of chronic arthritis. Thus, better treatment of immunodeficiency with prophylactic administration of gamma globulin and preventing infection may have lowered the incidence of arthritis in their cohort.

Dysfunction in other arms of the immune system also is associated with autoimmune disease. Complement deficiencies are associated with systemic lupus erythematosus; neutrophil and natural killer cell dysfunction are associated with hemophagocytic lymphohistiocytosis; combined variable immunodeficiencies are associated with granulomatous disease and immune cytopenias; T-cell deficiencies and Trisomy 21 with chronic arthritis and endocrinopathies and many autoinflammatory and very-early onset inflammatory bowel diseases with various forms of immunodeficiency (eg, deficiency of adenosine deaminase 2). Over the last 2 decades, there has been progress in the understanding of immune pathways. Monogenic inborn errors of immunity were recognized, both of the innate and the adaptive immune systems. These patients are not only susceptible to infectious organisms but have increased propensity for rheumatologic, autoinflammatory, malignant, and allergic manifestations due to dysregulation of the immune system. Occasionally, as suggested by the authors, immune complexes related to incompletely cleared infections can confer autoimmunity. We now understand that it is not only a ghost infectious pathogen causing the coexistence of hypogammaglobulinemia/other immunodeficiency and arthritis/autoimmunity, rather a common or connected dysregulated immune pathway (eg, nuclear factor kappa B). This understanding enables better diagnosis using genetic tests and, in many cases, better treatment.

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Table I. MRI data for brain regions, liver, and spleen over the course of study 250-901

Brain regions or organ		Nonaffected range*	Baseline	Week 24	Week 48	Statistics, baseline vs week 48†
Whole brain, mL	Mean	966-1331	1019	1029	1021	26-mL loss (−2.7%) on average;
	Median		1053	1023	1016	paired *t* test, $P = .0013$ (n = 20)
	Range		671-1241	819-1253	801-1247	
Cortical gray matter, mL	Mean	489-648	500	495	487	32-mL loss (−6.5%) on average;
	Median		502	491	493	paired *t* test, $P = .0003$ (n = 19)
	Range		326-610	372-626	367-611	
Cortical white matter, mL	Mean	303-459	325	335	336	3-mL gain (+0.5%) on average;
	Median		325	325	331	paired *t* test, $P = .64$ (n = 20)
	Range		191-421	268-469	259-460	
Cerebellum, mL	Mean	105-164	142	146	147	4-mL gain (+3.0%) on average;
	Median		138	142	144	paired *t* test, $P = .0004$ (n = 20)
	Range		114-174	127-178	121-178	
Cerebellar gray matter, mL	Mean	84-135	114	115	117	1-mL gain (+1.0%) on average;
	Median		112	114	114	paired *t* test, $P = .32$ (n = 20)
	Range		81-138	90-143	98-143	
Cerebellar white matter, mL	Mean	20-40	27	31	31	3-mL gain (+12.4%) on average;
	Median		27	28	29	paired *t* test, $P < .0001$ (n = 20)
	Range		19-37	23-51	21-41	
Ventricles, mL	Mean	5-30	24	27	32	8-mL gain (30.3%) on average;
	Median		21	23	26	paired *t* test, $P < .0001$ (n = 20)
	Range		10-53	10-61	11-71	
Cortical thickness, mm	Mean	2.36-3.07	2.68	2.68	2.60	0.16-mm loss (−5.8%) on average;
	Median		2.72	2.67	2.61	paired *t* test, $P = .0015$ (n = 20)
	Range		1.74-3.03	2.25-3.00	1.94-2.84	
Liver, L/m^2‡	Mean	0.55-0.85	1.33	1.31	1.39	0.06-L/m^2 gain (+4.5%) on average;
	Median		1.29	1.30	1.41	paired *t* test, $P = .0184$ (n = 14)
	Range		1.10-1.74	1.07-1.57	1.14-1.82	
Liver, mL	Mean	295-945	997	1059	1166	155-mL gain (+15.8%) on average;
	Median		986	1062	1133	paired *t* test, $P < .0001$ (n = 14)
	Range		573-1408	744-1417	874-1521	
Spleen, L/m^2‡	Mean	0.04-0.15	0.21	0.20	0.21	0.00-L/m^2 gain (+0.1%) on average;
	Median		0.21	0.20	0.20	paired *t* test, $P = 1.00$ (n = 14)
	Range		0.10-0.31	0.12-0.27	0.12-0.30	
Spleen, mL	Mean	25-140	160	163	176	15-mL gain (+14.1%) on average;
	Median		158	155	161	paired *t* test, $P = .0148$ (n = 14)
	Range		71-246	86-259	93-259	

*Regional brain volume ranges are the lowest and highest values obtained from 35 unaffected subjects aged 4-9 years and analyzed by the same investigator (Dr Igor Nestrasil[20]). Subjects in study 250-201 ranged in age from 1 to 9.5 years; past age 2 years, variability in cortical volumes among subjects with similar ages is greater than the volume increases in relation to chronological age.
†The youngest subject (13-month-old at entry) was excluded.
‡BSA-normalized liver and spleen volume ranges from unaffected subjects aged 2-9.5 years were estimated from previously published graphs.[19-21]

Table II. Subject characteristics: sex, age at diagnosis, and age at baseline

Characteristics		Age ≤6 y at diagnosis (N = 61)	Age >6 y at diagnosis (N = 4)
Sex, n (%)	Male	30 (49)	2 (50)
	Female	31 (51)	2 (50)
Age at diagnosis, mo			
Males	Mean	30	101
	Median	25	101
	Range	5-74	91-110
Females	Mean	41	147
	Median	39	147
	Range	3-77	137-156
Age at study baseline, mo			
Males	Mean	67	103
	Median	61	103
	Range	17-164	91-115
Females	Mean	64	162
	Median	53	162
	Range	12-162	39-184

Table IV. HS and HS-NRE concentrations over the course of study 250-901

Measurement times		Total HS, mg/L		HS-NRE, mg/L		Correlations
		CSF	Plasma	CSF	Plasma	
Baseline	Mean	0.486	0.806	0.150	0.082	Total HS, CSF vs plasma (n = 22): $r = 0.52$, $P = .01$
	Median	0.470	0.776	0.148	0.082	HS-NRE, CSF vs plasma (n = 21): $r = 0.47$, $P = .03$
	Range	0.301-0.762	0.426-1.310	0.065-0.314	0.043-0.140	Total HS vs HS-NRE, CSF (n = 22): $r = 0.93$, $P < .0001$
						Total HS vs HS-NRE, plasma (n = 21): $r = 0.86$, $P < .0001$
Week 24	Mean	0.506	0.812	0.152	0.082	Total HS, CSF vs plasma (n = 21): $r = 0.24$, $P = .28$
	Median	0.470	0.809	0.148	0.082	HS-NRE, CSF vs plasma (n = 21): $r = 0.31$, $P = .18$
	Range	0.311-0.883	0.482-1.358	0.079-0.353	0.048-0.137	Total HS vs HS-NRE, CSF (n = 21): $r = 0.92$, $P < .0001$
						Total HS vs HS-NRE, plasma (n = 22): $r = 0.87$, $P < .0001$
Week 48	Mean	0.498	0.751	0.152	0.079	Total HS, CSF vs plasma (n = 18): $r = 0.19$, $P = .43$
	Median	0.464	0.721	0.140	0.081	HS-NRE, CSF vs plasma (n = 18): $r = 0.50$, $P = .03$
	Range	0.261-0.834	0.345-1.358	0.065-0.374	0.037-0.137	Total HS vs HS-NRE, CSF (n = 19): $r = 0.91$, $P < .0001$
						Total HS vs HS-NRE, plasma (n = 19): $r = 0.77$, $P = .0001$
Nonaffected 95th percentile		0.148	0.323	0.010	0.015	

Nonaffected individuals (n = 91) had quantifiable levels of total HS ranging in plasma from 0.068 to 0.323 mg/L (9th-95th percentile), with CSF HS-NRE levels below the limit of quantification (ie, 0.005 mg/L) for the great majority of nonaffected subjects (n = 59).