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An observational, prospective, multicenter, natural history study of patients with mucopolysaccharidosis type IIIA

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ABSTRACT

Mucopolysaccharidosis type IIIA (MPS IIIA, also known as Sanfilippo syndrome) is a rare genetic lysosomal storage disease characterized by early and progressive neurodegeneration resulting in a rapid decline in cognitive function affecting speech and language, adaptive behavior, and motor skills. We carried out a prospective observational study to assess the natural history of patients with MPS IIIA, using both standardized tests and patient-centric measures to determine the course of disease progression over a 2-year period. A cohort of 23 patients (7 girls, 16 boys; mean age 28–105 months at baseline) with a confirmed diagnosis of MPS IIIA were assessed and followed up at intervals of 3–6 months; cognitive function was measured using Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) to derive cognitive development quotients (DQ). Daily living, speech/language development and motor skills were measured using the Vineland Adaptive Behavior Scale (VABS-II). Sleep–wake patterns, behavior and quality-of-life questionnaires were also reported at each visit using parent/caregiver reported outcome tools. All patients had early onset severe MPS IIIA, were diagnosed before 74 months of age, and had cognitive scores below normal developmental levels at baseline. Patients less than 40 months of age at baseline were more likely to continue developing new skills over the first 6–12 months of follow-up. There was a high variability in cognitive developmental age (DA) in patients between 40 and 70 months of age; two-thirds of these patients already had profound cognitive decline, with a DA ≤10 months. The highest cognitive DA achieved in the full study cohort was 34 months. Post hoc, patients were divided into two groups based on baseline cognitive DQ (DQ ≥50 or <50). Cognitive DQ decreased linearly over time, with a decrease from baseline of 30.1 and 9.0 points in patients with cognitive DQ ≥50 at baseline and cognitive DQ <50 at baseline, respectively. Over the 2-year study, VABS-II language scores declined progressively. Motor skills, including walking, declined over time, although significantly later than cognitive decline. No clear pattern of sleep disturbance was observed, but night waking was common in younger patients. Pain scores, as measured on the quality-of-life questionnaire, increased over the study period. The findings of this study strengthen the natural history data on cognitive decline in MPS IIIA and importantly provide additional data on endpoints, validated by the patient community as important to treat, that may form the basis of a multidomain endpoint capturing the disease complexity.

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development (3rd edition); CA, chronological age; CSHQ, Children's Sleep Habit Questionnaire; DA, developmental age; DQ, developmental quotient; HS, heparan sulfate; ITQOL, Infant Toddler Quality of Life questionnaire; MPS IIIA, mucopolysaccharidosis type IIIA; QoL, quality of life; SGSH, sulfoglucosamine sulfohydrolase; VABS-II, Vineland Adaptive Behavior Scale (2nd edition).

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1. Introduction

Mucopolysaccharidosis type III (MPS III), also known as Sanfilippo syndrome, is a rare lysosomal storage disease, defined by four subtypes (MPS IIIA, MPS IIIB, MPS IIIC, and MPS IIID) [1]. MPS IIIA has an estimated birth prevalence of between 0.26 and 1.89 per 100,000 live births, depending on the population studied [2] and is caused by a recessive genetic defect of a lysosomal sulfamidase, N-sulfoglucosamine sulfohydrolase (SGSH) [1]. SGSH is ubiquitously expressed within tissues and is essential for degradation of heparan sulfate (HS). Deficits in SGSH result in the accumulation of toxic levels of partially degraded oligosaccharides [1]. After a short period of normal development, MPS IIIA manifests as a severe neurodegenerative disease with progressive developmental regression, resulting in severe cognitive deficits combined with relatively milder somatic symptoms and a poor deteriorating quality of life (QoL) [3]. The majority of patients have the severe form of MPS IIIA, in which symptoms typically appear between 1 and 3 years of age, presenting initially as slowed cognitive development, and a delay in meeting major developmental milestones, particularly relating to speech. Most children with MPS IIIA do not exceed a cognitive age greater than 30–35 months and develop severe behavioral problems, loss of speech, and progressive cognitive decline [4–6]. Other commonly reported symptoms include sleep difficulty, hearing and vision problems, epilepsy, recurrent diarrhea, and frequent ear and nose infections [3,5,7]. In their teenage years, patients continue to experience decline in all motor functions, culminating in complete loss of locomotion, dysphagia, and pyramidal tract lesions [7–9]. Most patients die in their second decade of life; the average age of survival is 15 years [3,4,7,10].

There is currently no approved disease-specific treatment for MPS IIIA, although novel therapies are being developed. In this context, a more detailed understanding of the natural disease course of MPS IIIA is essential to design studies that are able to appropriately assess the efficacy of new treatments, particularly on the progression of central nervous system and cognitive symptoms. In complex diseases, it can be difficult to identify a single relevant clinical endpoint that can sufficiently capture the change in disease status induced by treatment. Three previously reported natural history studies of MPS IIIA have assessed change in developmental quotient (DQ) and/or cognitive decline over time [6,7,11], but little has been published on other endpoints. Regulatory authorities have highlighted the importance of identifying and capturing data on disease-specific, patient-centric outcome measures that can assess longitudinal changes in the complexity of the progressive neurological manifestations of MPS IIIA, such as delay/loss of speech, loss of mobility, and sleep disturbance.

This paper reports the findings of a prospective observational cohort study conducted to document the natural history and disease course of patients with MPS IIIA over a 2-year period. The objectives of the study were to evaluate clinical progression in patients with MPS IIIA who had not received any disease-specific treatment, and to capture standardized data from assessments, not only of cognitive development, but also multidomain measurements of behavioral capabilities which include daily living skills, such as eating, sleep–wake habits, and the effect of MPS IIIA on the QoL of patients and their families, including measures for pain. The study was designed to provide control natural history data for subsequent clinical studies of new treatments for MPS IIIA, and was also designed such that the data could be merged with data from other ongoing or published studies on the natural history of MPS IIIA.

2. Material and methods

2.1. Study design

The study was a multinational, prospective, descriptive longitudinal cohort study designed to provide data on the natural disease course of MPS IIIA over a 2-year time period. All patients were prescreened for eligibility. Eligible patients were invited to participate in the study at one of five participating study centers (Brazil, France, Germany, the Netherlands, and the United Kingdom). The study consisted of six onsite visits, including screening, baseline (assessment Day 0), and at 6 months (±14 days), 12 months (±14 days), 18 months (±14 days), and 24 months from baseline or end-of-study visit (±14 days).

2.2. Patients

All eligible patients had a confirmed, documented diagnosis of MPS IIIA, were aged ≤9 years and medically stable enough to adhere to the study protocol, and had written informed consent from parents or legal guardians in accordance with local regulations. Exclusion criteria were as follows: patients currently receiving any potential disease-modifying medicinal product or taking high-dose synthetic genistein (>100 mg/kg/day); patients who had received a hematopoietic stem cell/bone marrow transplantation; patients who participated in clinical trials and were receiving gene therapy or enzyme replacement therapy; patients homozygous or compound heterozygous for the p.Ser298Pro mutation (c.892 T > C); patients with confounding unrelated serious comorbidities (e.g. Down's syndrome); and patients whose visual or hearing impairment prevented cooperation with the selected neurodevelopmental assessments.

2.3. Assessments

The screening visit included a genotype assessment (if not already available), an enzyme activity analysis, a physical examination, and a neurological examination. Baseline assessments included a cognitive and behavioral assessment using the Bayley Scales of Infant and Toddler Development (3rd edition) (BSID-III) [12], assessment of adaptive behavior using the Vineland Adaptive Behavior Scales (VABS-II) [13], completion of patient and parent QoL questionnaires using the Infant Toddler Quality of Life questionnaire (ITQOL) [14], and semi-structured interviews of parents/caregivers. The MPS IIIA-related medical history of each patient was taken at baseline and included mutation analysis, age at diagnosis, clinical manifestations and symptoms, cognitive and motor milestones, behavioral problems, and sleeping problems. A physical and neurological examination was also completed at baseline.

The following variables were used as study endpoints. The change from baseline in cognitive function using the BSID-III; change from baseline in adaptive behavioral composite standard score measured using VABS-II; longitudinal description of sleep disturbances (using the Abbreviated Children's Sleep Habits Questionnaire (CSHQ), a parent-rated child sleep habits questionnaire comprised of 22 questions grouped into the eight domains: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing, and daytime sleepiness [15], and a sleep diary); and assessment of patient's and parents' QoL using ITQOL for pain scores and semistructured parental/caregiver interviews. DQ was calculated by dividing the patient's developmental age (DA) by their chronological age (CA) and expressed as DA/CA multiplied by 100 (to remove any potential "floor" effects of standardized scores applied to severely cognitively impaired patients).

The endpoints assessed were selected as they all represent key domains which parents/caregivers have reported as important symptoms of MPS IIIA to be targeted with future therapies [16].

2.4. Statistical methodology

As this was a descriptive cohort study, there were no planned or conducted efficacy analyses. An interim analysis was performed after the 12-month study visit, and the final analysis was performed after the last patient completed their 24-month visit.

Individual patient profiles were plotted over time. Continuous variables are reported as mean (standard deviation [SD]), median

(minimum–maximum values) and 1st and 3rd quartiles. For categorical variables, the frequency and percentage of patients in a particular category were reported, and graphical techniques were used to assess patient trends over time. Correlations were calculated using the Pearson correlation in Excel.

The existence of a high-quality published natural history study [6] using the BSID-III allowed merging of data to produce a meta-analysis of 42 patients with the severe form of MPS IIIA.

3. Results

3.1. Patient disposition

The study population consisted of 23 patients (16 males and 7 females). All enrolled patients had baseline data and were included in subsequent endpoint analyses. Overall, 17 patients completed the study and were followed for 24 months. Patient demographics and baseline characteristics are presented in Table 1. The mean (SD) age at enrollment was 60.7 (23.9) months. All 23 patients in the study had early symptomatic onset MPS IIIA, had been diagnosed before 74 months of age (median 37.4 months) and were described as having the severe MPS IIIA disease phenotype. The time to diagnosis ranged from 1.4 to 57.4 months, highlighting the significant diagnostic delays that are often experienced by families of patients with the disease.

Most of the mutations identified in patients in this cohort were missense and had previously been described as pathogenic (Table 2) [34]. All the patients had severely reduced SGSH enzyme activity at baseline and 10 patients had no detectable residual enzyme activity. In total, 12 of the 23 patients were homozygous for their mutation. Most mutations were previously reported to be related to a rapidly progressing (severe) phenotype, while 7 variants have not been previously reported, of whom 3 (duplication, insertion and frameshift) were classified as (likely) severe and probably associated with a rapidly progressing phenotype (Table 2). One mutation was previously reported in two patients. However, information on the clinical phenotype of these patients was not available.

Six patients withdrew from the study before completion. Three of these six patients were withdrawn due to parental decision, mainly because of the additional burden of participating in the natural history study with severe disease. The other three patients were lost to follow-up. Overall, 19 patients were followed up for 12 months and 17 patients were followed up for 24 months.

3.2. Cognitive assessment

All 23 patients in the cohort had cognitive scores below average developmental levels for their age (Table 2). Patients less than 40 months of age at baseline were more likely to continue developing new skills over the first 6–12 months of follow-up. Two thirds of patients between 40 and 70 months of age were already demonstrating profound cognitive decline, with a DA lower than or equal to 10 months of age. The findings in our cohort of patients are very similar to the natural history data from a US cohort of patients with MPS IIIA published by Shapiro et al., in which BSID-III was also used to assess cognitive development over time [6]. As both the US study cohort and our study cohort were similar, and both used the BSID-III, we pooled the data from the two cohorts to provide a picture of the course of cognitive decline over time in a larger cohort (Fig. 1A).

The patients in this study were sorted post hoc into two groups, based on their cognitive DQ at baseline. Seven patients with a DQ ≥50 at baseline were all less than 50 months of age, while the age of the 16 patients with a DQ <50 at baseline ranged from 40 to 105 months. Analyses were conducted separately in these two groups. The mean cognitive DQ at baseline was 58.9 and 19.2 for the DQ ≥50 and DQ <50 groups, respectively (**Supplementary Table S1**). DQ decreased linearly over time, with decreases from baseline of 30.1 and 9.0 points in patients with cognitive DQ ≥50 at baseline and cognitive DQ <50 at baseline, respectively, who completed the 24-months follow-up (Fig. 1B). The highest cognitive DA achieved in the cohort was 34 months.

Table 1
Baseline characteristics of patients

Characteristic	Patients ($N = 23$)
Age at enrollment (months)†	60.7 ± 23.9 [27.9; 104.9]
Age at enrollment, n (%)	
<30 months	1 (4.4)
30–60 months	13 (56.5)
>60 months	9 (39.1)
Sex, n (%)	
Female	7 (30.4)
Male	16 (69.6)
Age at diagnosis (months)†	36.5 ± 17.7 [5.4; 74.7]
Time since diagnosis (months)†	24.2 ± 16.4 [1.4; 57.4]

Baseline patient characteristics in a cohort of 23 patients with mucopolysaccharidosis type IIIA.
† Results are presented as mean ± standard deviation and [minimum; maximum] values.

3.3. Speech development/loss of language

In this study, we used several assessment tools to collect data on speech and language: the language domain for BSID-III and the communication domain for VABS-II. We observed a strong correlation between VABS-II and BSID-III expressive language, and receptive language, with correlations of 0.90 and 0.80, respectively (**Supplementary Fig. S1**). There was also a strong correlation of 0.86 between BSID-III expressive language and receptive language and a strong correlation of 0.77 between VAB-II expressive language and receptive language.

In receptive language, measured by VABS-II, most patients scored between 30 and 60 points (raw score) up to 80 months of age, and after 80 months of age, the raw scores for all patients had dropped to below 30 points (Fig. 2A). At baseline, the maximum raw score for receptive language was 59 points (the total potential raw score points for receptive language in the communication domain is 108). These patients had the ability to respond to a noise or their name, follow simple instructions, point to body parts and engage in basic listening for up to 5 minutes. A loss of 15 points, one SD (coincidentally the same SD for the publisher's norm-referenced communication domain standard score), signified a loss of ability for basic listening and to follow any complex instruction. Consistent with the observed maximum cognitive DA of 34 months, no child in this study had the ability to identify left and right or listen to a story for 30 minutes. At the lower end of the scale, patients only maintained the ability to respond to a noise and turn their head upon their name being called.

In expressive language, measured by VABS-II, two patients achieved raw scores between 150 and 190 (the total potential raw score points for expressive language is 308), retaining the ability to ask questions and use simple grammatical forms (Fig. 2B). However, most patients never exceeded a raw score of 100 points and their language development included being occasionally able to articulate initial consonants, a vocabulary of up to 50 words, and the ability to name people. As the disease progressed, patients only maintained the ability to vocalize needs and smile when spoken to. In these patients, receptive language and expressive language as measured by the VABS-II tracked a similar path to cognition as measured by BSID-III (Figs. 3 and 4).

The change in VABS-II language DQ and BSID-III cognitive DQ by CA was plotted (Fig. 3) showing a cognitive decline parallel to language decline.

3.4. Motor skills/walking

Two different tools were used to collect data on the motor skill of walking (part of the gross motor assessment): the BSID-III gross

Table 2
Demographic data of participants

Patient	Mutation 1	Mutation 2	Allele 1 Predicted phenotype	Allele 2 Predicted phenotype	Allele 1/Allele 2 Predicted phenotype	Sex	Age at diagnosis (mo)	Age at baseline (mo)	BSID-III cognitive DA at baseline/6mo/12mo/18mo/24mo†	BSID-III cognitive DQ at baseline/6mo/12mo/18mo/24mo†	VABS-II cognitive DA at baseline/6mo/12mo/18mo/24mo†	VABS-II cognitive DQ at baseline/6mo/12mo/18mo/24mo†
1	c.1136_1139dupTGCA	c.1136_1139dupTGCA	?, u, P:RP	?, u, P:RP	RP/RP	M	16	31	18/17/19/19/18	60/47/45/39/33	17/21/23/25/29	57/58/55/52/54
2	c.535G>A (p.Asp179Asn)	c.1144_1145InsAGCGCC (p.Arg382_His383insGlnArg)	RP [17,18]	?, u, P:RP	RP/RP	M	28	48	8/5/5/5/8	17/9/8/8/11	13/16/17/12/13	28/30/38/18/18
3	c.877C>T (p.Pro293Ser)	c.1144_1145insAGCGCC (p.Arg382_His383insGlnArg)	RP [19,20]	?, u, P:RP	RP/RP	M	9	40	5/10/9/13	13/22/17/22	14/11/16/16/16	36/24/31/28/25
4	c.734G>A (p.Arg245His)	c.734G>A (p.Arg245His)	RP [3,20–28]	RP [3,20–28]	RP/RP	M	44	47	20/27/26/22/17	57/52/45/34/24	31/29/36/35/29	66/56/62/55/41
5	c.1297C>T (p.Arg433Trp)	c.1297C>T (p.Arg433Trp)	RP [20,25,27,29,30]	RP [20,25,27,29,30]	RP/RP	M	53	80	11/11/12/10/8	14/13/13/10/8	18/17/19/18/17	23/20/21/18/17
6	c.734G>A (p.Arg245His)	c.734G>A (p.Arg245His)	RP [3,20–28]	RP [3,20–28]	RP/RP	M	47	58	26/25/25/24/23	45/39/36/32/28	23/20/19/21/18	40/31/27/28/22
7	c.571G>A (p.Gly191Arg)	c.734G>A (p.Arg245His)	RP [3,27]	RP [3,20–28]	RP/RP	M	39	96	7	7	14	15
8	c.734G>A (p.Arg245His)	c.734G>A (p.Arg245His)	RP [3,20–28]	RP [3,20–28]	RP/RP	F	75	102	11/11/11/8/7	11/10/10/7/6	11/11/8/11/10	11/10/7/9/8
9	c.220C>T (p.Arg74Cys)	c.734G>A (p.Arg245His)	RP [3,17,18,20,22,23,25–28,31,32]	RP [3,20–28]	RP/RP	F	37	46	25/27	54/51	34/30	74/57
10	c.197C>G (p.Ser66Trp)	c.734C>A (p.Arg245His)	RP [3,17,20,21,23,25,26,30,32,33]	RP [3,20–28]	RP/RP	M	55	75	9	12	10/12	13/15
11	c.1167C>A (p.Asn389Lys)	c.1167C>A (p.Asn389Lys)	? [3,22]	? [3,22]	?/?	M	16	49	20	41	20	41
12	c.1080delC (p.Val361Sfs*52)	c.1135delG (p.Val361Sfs*52)	RP [3]	RP [3]	RP/RP	M	38	38	25/28/24/13	66/64/48/23	25/34/33/22/19	66/77/66/39/31
13	c.80delT (p.Leu27Rfs*237)	c.734G>A (p.Arg245His)	?, u, P:RP	RP [3,20–28]	RP/RP	M	50	51	29/34/29/32	58/61/47/43	29/37/31/33/37	58/66/50/48/50
14	c.800 T>C (p.Leu267Pro)	c.800 T>C (p.Leu267Pro)	?, u, NP	?, u, NP	?/?	M	6	45	25/24/19	56/42/28	32/27/32/29/21	71/53/56/46/30
15	c.448C>T (p.Arg150Trp)	c.448C>T (p.Arg150Trp)	RP [25,30]	RP [25,30]	RP/RP	F	26	40	10/13/12/8/5	26/29/24/14/7	NA/23/18/18/11	NA/51/35/31/17
16	c.197C>G (p.Ser66Trp)	c.1160 T>G (p.Val387Gly)	[3,17,20,21,23,25,26,30,32,33]	?, u, NP	RP/?	M	63	89	8/8/11/12/8	9/8/11/11/7	18/16/14/16/10	20/17/14/15/9
17	c.733C>T (p.Arg245Cys)	c.734G>A (p.Arg245His)	?, u, NP	RP [3,20–28]	?/RP	M	45	98	5/7/6/10/5	5/7/5/9/4	16/16/14/16/14	16/15/13/14/11
18	c.1139A>G (p.Gln380Arg)	c.1139A>G (p.Gln380Arg)	RP [3,23]	RP [3,23]	RP/RP	F	44	62	25/25/20/13/3	40/37/27/16/4	26/24/25/19/11	42/35/34/24/13
19	c.734G>A (p.Arg245His)	c.1080delC (p.Val361Sfs*52)	RP [3,20–28]	RP [3]	RP/RP	F	51	105	10/12/16/14/13	10/11/14/11/10	11/12/16/16/13	11/11/14/13/10
20	c.1080delC (p.Val361Sfs*52)	c.1080delC (p.Val361Sfs*52)	RP [3]	RP [3]	RP/RP	M	19	48	8/8/10/11	17/15/17/16	18/18/19/20	38/34/32/30
21	c.1080delC (p.Val361Sfs*52)	c.1080delC (p.Val361Sfs*52)	RP [3]	RP [3]	RP/RP	F	36	71	7/7/5/3	10/9/6/3	9/9/8/7	13/12/10/8
22	c.734G>A (p.Arg245His)	c.734G>A (p.Arg245His)	PR [3,20–28]	RP [3,20–28]	RP/RP	M	26	28	17/22/19/15	63/67/49/29	19/23/25/20	70/70/64/39
23	c.1122C>A (p.Pro374Pro)	c.1080delC (p.Val361Sfs*52)	?, u, NP	RP [3]	?/RP	F	20	46	14/18/15/13/10	31/35/26/20/14	17/17/15/24/16	38/33/26/38/23

Genotype and cognitive DA and DQ (measured using the Bayley Scales of Infant and Toddler Development [3rd edition] (BSID-III) or the Vineland Adaptive Behavior Scale (VABS-II)) compared with baseline age per individual patient. DA, developmental age; DQ, developmental quotient; mo, months; NP = no phenotype predicted; P:RP = predicted rapidly progressing (severe) phenotype based on mutation; RP = rapidly progressing (severe) phenotype; u = previously unreported variant;? = unknown phenotype.

† The number of values differ depending upon the length of patient follow-up.

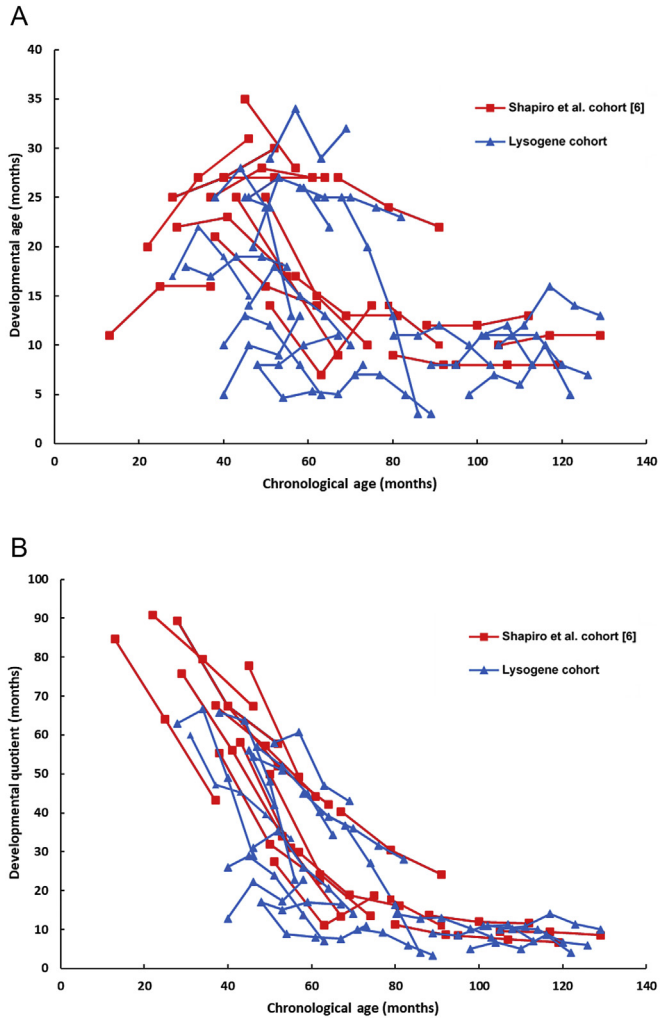

Fig. 1. Evolution of developmental age (A) and developmental quotient (%) (B) by chronological age in patients with mucopolysaccharidosis type IIIA. Change assessed using the Bayley Scales of Infant and Toddler Development (3rd edition). Data have been merged with those of Shapiro et al. [6].

motor domain (**Supplementary Fig. S2**) and VABS-II gross motor domain. A strong correlation of 0.86 was observed between DA based on the gross motor score of the VABS-II and DA based on the gross motor score of the BSID-III. The VABS-II gross motor domain collects clusters of data for sitting, beginning mobility, beginning to stand or walk, throwing a ball, climbing, running, using stairs, jumping, walking places, riding a bike, lifting and carrying, and stamina. However, not all of these clusters are relevant for capturing changes in walking for children with MPS IIIA; therefore, in order to focus purely on walking in these patients, we identified four clusters of questions in the VABS-II questionnaire which were most informative for walking skills: these were clusters C (beginning to stand and walk), F (running), G (using stairs) and I (walking places) (the maximum score for these domains together is 80). There was a strong correlation between VABS-II gross motor subdomain score (Fig. 5A) and VABS-II walking clusters score (Fig. 5B) of 0.92. Until 60 months of age, patients had a raw score for the VABS-II walking clusters combined between 40 and 78 points. One patient reached a maximum score of 80 points at 74 months of age. A score of 40 to 50 means that the child has lost the ability to run smoothly and will have frequent falls; they will not have the ability to ascend or descend stairs with alternating feet. After 60 months of age, patients walking motor skills may dramatically decline and they may lose the ability to walk. In this cohort, a dramatic decline in walking skills was seen in five patients, whilst the others remained stable.

The data show that although cognition and gross motor function decline at a similar rate, gross motor function is preserved for a significantly longer period compared with cognition (Fig. 6).

3.5. Sleep

Sleep was assessed using an abbreviated form of the CSHQ [15] and Actiwatch (wearable device capturing movement during sleep). Actigraphy data showed a high variability among patients and within a patient. In our cohort of MPS IIIA patients, it was not possible to identify a specific sleep pattern, despite reports of sleep disorders in the medical history of 61% of the population enrolled. From baseline to month 24, patients tended to sleep 81.0 minutes less, spend 33 fewer minutes in bed, and took on average 5 minutes longer to fall asleep. Similarly, at month 24 compared with baseline, patients spent 48 more minutes awake at night. During the day, patients took fewer naps on average at month 24 than baseline for nearly an hour less in total duration. Sleep efficiency was high at baseline (>95%) and fell by 10 points over the course of the study (85% at month 24). The nighttime fragmentation index (total number of awakenings/shifts divided by the total sleep time in hours) remained stable while the daytime fragmentation index (marker of daytime sleepiness) dropped steadily from an average of 7 at baseline to 1.0 ± 3.3 at month 24.

Data from the CSHQ in the study cohort showed that night waking was a more prevalent issue faced by caregivers and parents compared with the other sleep score subdomains. High inter- and intra-patient variability was observed in night waking scores over time (Fig. 7). However, in patients with a DQ <50 at baseline, night wakings became less during the study (Fig. 7) (Table 3). Sleep was reported as not only a challenge for the child, but also for the family. Parents reported that sleep was a very important issue at some point in their child's history, which heavily impacted the family throughout the disease course.

3.6. Pain

The instrument used to measure pain was the ITQOL, a 47-item questionnaire that assesses the physical, cognitive, and social well-being of the child, and the impact of the child's illness on parent/caregiver's QoL. The ITQOL calculates scores in 12 domains, of which two questions address the pain/discomfort domain. Scores range from 0 (worst health level) to 100 (best possible health level).

- Question 4.1: During the past 4 weeks, how intense was the bodily pain or discomfort?
- Question 4.2: During the past 4 weeks, how often has your child had discomfort or pain anywhere in his/her body?

Patients in this study cohort who had a baseline DQ ≥50 had a similar mean ITQOL score to the general population (82 and 83.8, respectively). In this study, pain appeared to worsen over time and in the older population of more impaired children. Patients with a baseline cognitive DQ <50 at baseline had a mean score of 74 (**Supplementary Fig. S3**).

3.7. Eating

Four clusters of questions from the daily living skills personal domain of the VABS-II survey were identified that specifically relate to eating: clusters A (beginning to eat), C (drinking), E (using eating utensils), and K (using table knife). The maximum raw score for these clusters was 54. There was a strong correlation between VABS-II daily living skills domain and VABS-II eating clusters of 0.86. In patients with a baseline cognitive DQ ≥50, the mean raw score for the eating cluster was 36 and for patients with a baseline cognitive DQ <50 it was 27. The change in VABS-II eating score by CA is shown in Fig. 8; a decrease in raw score from 36 to 27 signified the loss of capacity to use eating utensils.

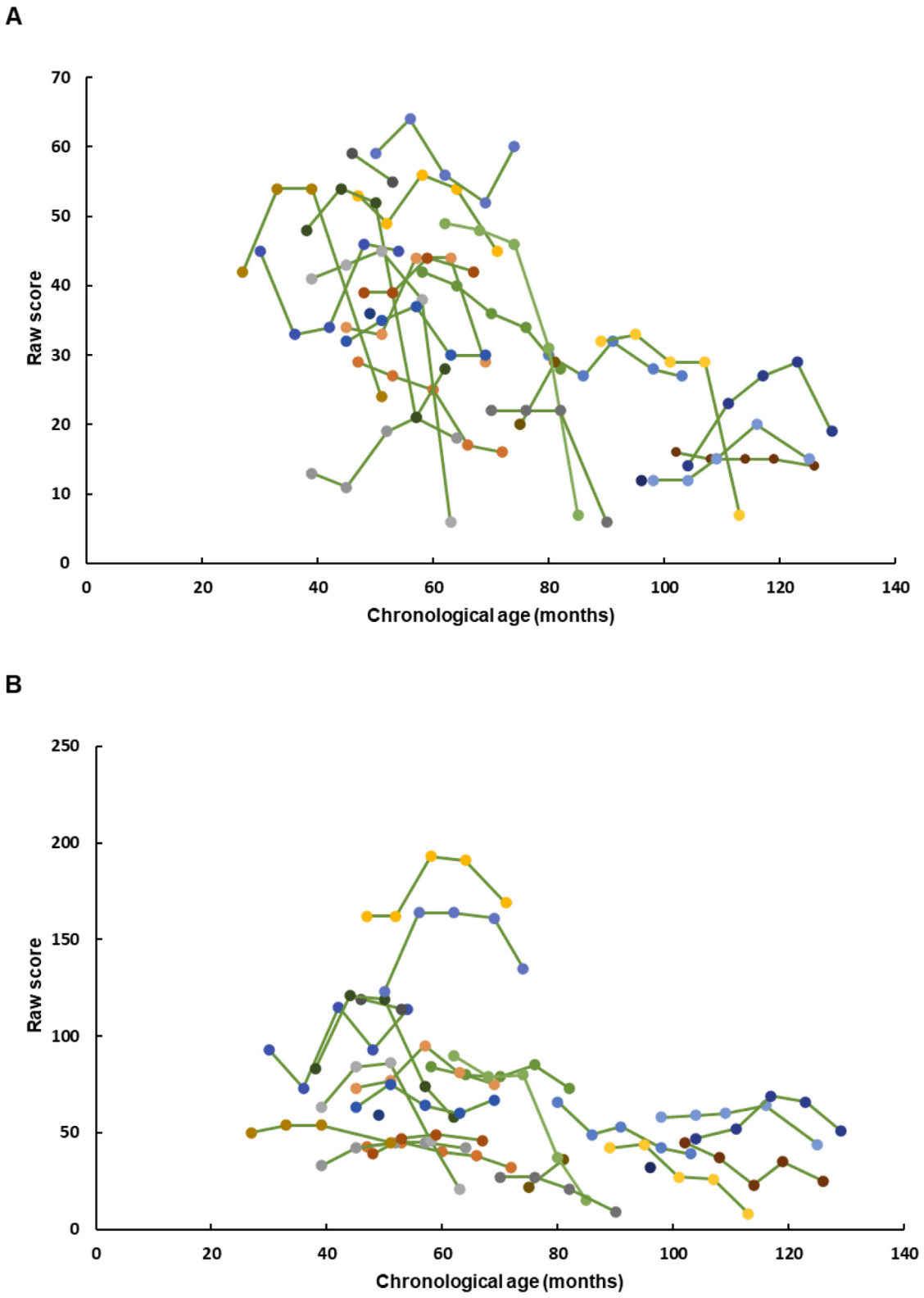

Fig. 2. Change in Vineland Adaptive Behavior Scale (VABS-II) for receptive language (A) expressive language (B) by chronological age.

4. Discussion

In patients with MPS IIIA, neurological dysfunction and rapid cognitive decline are hallmarks of the disease. The central nervous system manifestations of these conditions are devastating to the affected child and their family, and result in premature death, usually in the second decade of life. This multicenter, prospective observational study describes the natural history of MPS IIIA over a 2-year period in a cohort of 23 patients with the severe form of MPS IIIA, with the aim of expanding knowledge on the course of the disease and identifying

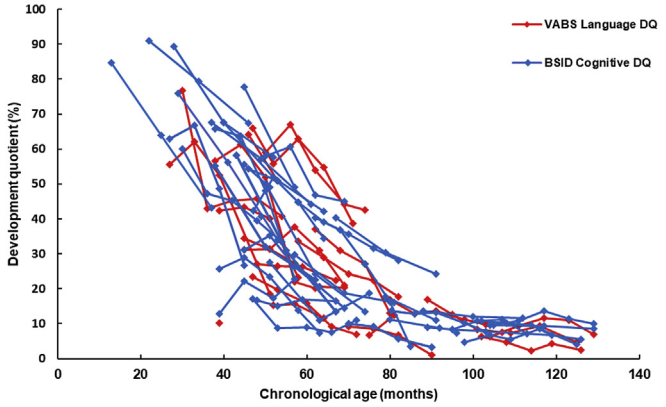

Fig. 3. Change in Vineland Adaptive Behavior Scale (VABS-II) language DQ (%) and Bayley Scales of Infant and Toddler Development (BSID-III) cognitive DQ (%) score by chronological age. DQ, developmental quotient.

suitable endpoints, other than DQ, and on patient-centric outcome measurement tools for use in future clinical trials. All patients in our cohort had early onset, severe MPS IIIA and had cognitive development levels below those expected for their age. The majority of patients had a DA of less than 10 months. Over the 2-year study period, we observed a progressive decrease in patients' DQ (derived from BSID-III scores), speech and language skills, and motor/walking skills (obtained using domains of the VABS-II). In this population of predominantly European patients, we observed that cognitive function and language function essentially have the same timing and slope of decline. Although in everyday practice an arrest in language development usually is the first obvious clinical sign, before an arrest in cognitive development, this might be caused by ascertainment bias, as cognitive testing is often not performed early in the life of the patient. In our study, similar changes in cognitive function were observed compared with the published data from the three other natural history studies of MPS IIIA patients that have reported changes in cognitive development and its impact on patient behavior and motor development [6,7,11]. The retrospective analysis by Buhrman et al. of a cohort of 21 boys and 25 girls with MPS IIIA identified early and significant language developmental delay and hearing loss followed by a rapid decline in cognitive skills and adaptive behavior after 3 years of age; parents reported that the children had multiple behavioral and sleep difficulties during the period of cognitive decline [7]. Two prospective natural history studies confirmed these findings and explored the outcome measures most

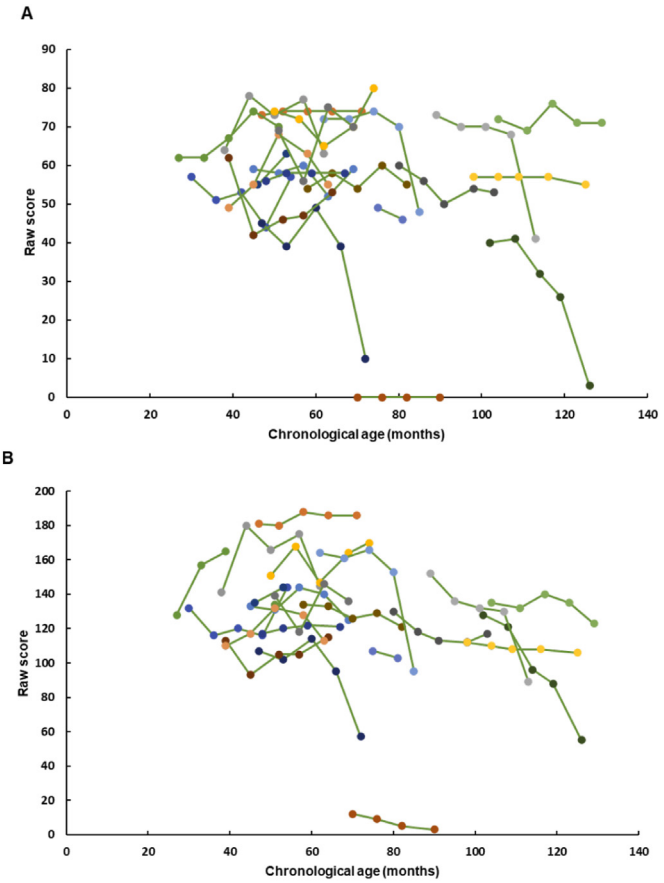

Fig. 5. Change in Vineland Adaptive Behavior Scale (VABS-II) gross motor score (A) and VABS-II gross motor walking (clusters C + F + G + I) score (B) by chronological age.

suitable for assessing changes in cognition in MPS IIIA patients. Truxal et al. studied a US cohort of 15 patients with MPS IIIA [11] and used Leitner-R/Mullen scales to show that cognitive development peaked at 30–36 months of age then declined over a 6-month interval; similar to our study, the VABS-II composite scale and the Child Behavior Checklist questionnaire were used to measure adaptive behavior which showed significant decline over the study [11]. The third study, published by Shapiro et al., prospectively studied a US cohort of 25 patients with a diagnosis of MPS IIIA over a 2-year period and assessed cognitive

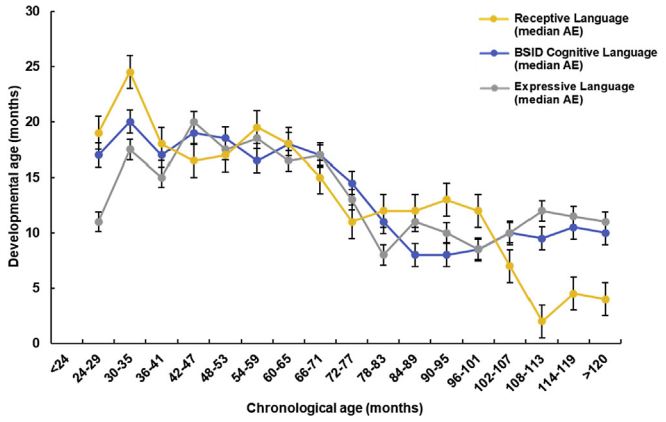

Fig. 4. Change in Bayley Scales of Infant and Toddler Development (BSID-III) cognitive language developmental age, receptive language developmental age, and expressive language developmental age median scores by 6-month intervals of chronological age. AE, age equivalent.

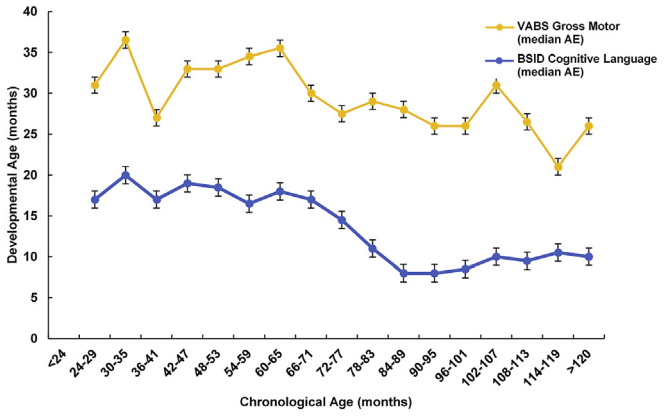

Fig. 6. Change in Vineland Adaptive Behavior Scale (VABS-II) gross motor median scores compared with change in Bayley Scales of Infant and Toddler Development (BSID-III) cognitive language median scores by 6-month intervals of chronological age. AE, age equivalent.

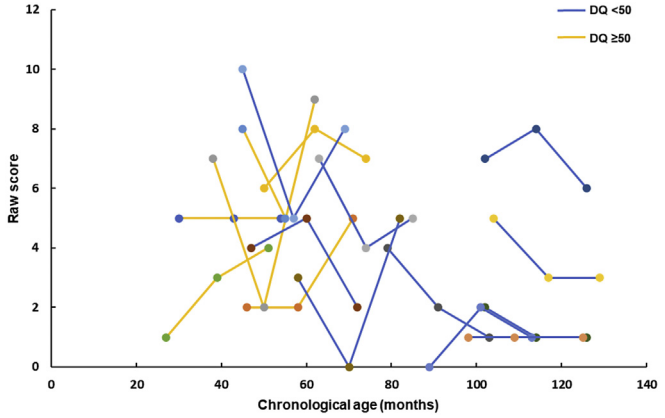

Fig. 7. Change in night waking score (12 + 17 + 18) by chronological age and DQ of ≥50 and <50. DQ, developmental quotient.

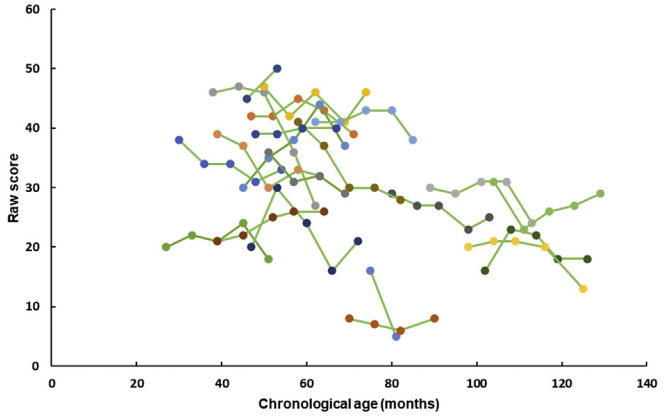

Fig. 8. Change in Vineland Adaptive Behavior Scale (VABS-II) eating score by chronological age.

development using the BSID-III and VABS-II scales to derive DA and DQ using the same methodology as we used in our study. Shapiro et al. reported a dramatic slowing of DQ over time, particularly in patients with the severe form of the disease [6]. They also reported a decline in DQ of 14.6 points per year in severe patients and 3.7 points per year in slowly progressing patients. To expand knowledge of the natural history of cognitive decline in MPS IIIA patients, we decided to merge our BSID-III data on DA and DQ according to CA with the Shapiro US cohort data. The two studies used the same methods to assess cognitive decline and this has expanded knowledge on the natural disease course and suitability of the DQ as an outcome measure by providing a larger dataset. Data from the two studies were only pooled for the analysis of overall cognitive development by age; other endpoints were analyzed separately for our study cohort only.

Data from patients from our natural history cohort were sorted post hoc into two groups depending on their cognitive DQ at baseline. The threshold of DQ 50 was selected as it was the minimum DQ required to see differences in this study, as well as outcomes for future clinical trials, including the currently ongoing intracerebral gene therapy study (ClinicalTrials.gov Identifier: NCT03612869). In addition, the DQ shows a floor effect at levels below 25%. The seven patients with a cognitive DQ ≥50 at baseline were <50 months old, while patients with a cognitive DQ <50 at baseline age ranged from 40 to 105 months. In patients with a lower DQ, the cognitive decline appeared to reach a nadir (or floor) at around 70 months of age and thereafter remained relatively stable over the 2-year period of follow-up in the study. In the older patients in the population, cognitive scales seem to lack sensitivity to detect progression of cognitive impairment. Overall, DQ follows a linear decrease over the course of the disease, though with different slopes of decline between the group of patients with cognitive DQ ≥50 at baseline and the group with cognitive DQ <50 at baseline. In the subgroup of patients with cognitive DQ ≥50 at baseline, cognitive DQ declined more rapidly over the 2-year follow-up period than in those with DQ <50. This is due to a flooring effect, of around 10 points, on the BSID-III score, apparently due to low sensitivity to change in profound cognitive impairment; so those with a DQ <50 will reach this floor sooner and will have a seemingly less rapid decline (when expressed as loss of DQ per time interval). The decline in speech and language skills followed the same slope as cognitive decline for the patients, while motor function was preserved for longer. A similar trend was also reported in the retrospective natural history study of Buhrman et al. [7] who also observed that motor function is preserved for a longer time than speech. These clinical observations highlight that future treatment may need to be administered in patients before the onset of this steep cognitive decline for optimal outcomes.

Studies of motor function in MPS IIIA patients are limited by the impact that cognitive deficits ultimately have in limiting patients' ability to comply with some tests of motor function. A potentially important finding of this study is that we showed that the overall gross motor domain of the VABS-II strongly correlated with the scores from the cluster of VABS-II questions that specifically related to walking, thereby validating the use of VABS-II gross motor domain scores as a relevant outcome measure for motor development in MPS IIIA that captures the key skill of walking.

Additionally, a longer preservation of gross motor function relative to cognition and language skills was observed in this study. This has important implications with regard to parents/caregivers, where reports of safety of the patients is a concern. This is in part due to the patients' hyperactivity and lack of fear continuously being expressed when motor functions allow for it. The patients' loss of cognitive and communication skills then creates further challenges with safety training and management.

The use of patient-focused outcome measures is strongly encouraged in studies of MPS, as parent/caregiver experience and proxy-reported patient experience data are now recognized by regulatory bodies as providing potentially important additional information on

Table 3
Child Sleep Habits Questionnaire sleep scores for night waking on 5-point scale.

Subscale item	MPS IIIA DQ <50 at baseline (n = 10)			MPS IIIA DQ ≥50 at baseline (n = 6)		
	Baseline	Month 12	Month 24	Baseline	Month 12	Month 24
Mean age (years)	6.0	7.0	8.1	3.3	4.3	5.2
Night wakings	4.3	3.3	3.3	5.2	4.2	6
Q12 Moves to other's bed in night	0.5	0.3	0.3	1.3	1.2	2.6
Q17 Awakes once during night	1.7	1.8	1.9	2	1.8	2.2
Q18 Awakes more than once	2.1	1.2	1.1	1.8	1.2	1.2

DQ, developmental quotient; MPS IIIA, mucopolysaccharidosis type IIIA; Q, question.

disease progression and (for clinical trials) response to treatment [35]. For this reason, although we used the BSID-III to assess cognitive decline, we reported VABS-II scores rather than BSID-III data for speech/language assessment and motor skills. The VABS-II questionnaire collects data outside of the clinical setting, and has a range of more specific questions (including parent/caregiver questions) that allows more details to be captured on the family experience of living with MPS IIIA. The VABS-II questionnaire may also remove the challenges with performance-based testing in novel environments for children with MPS IIIA, and rather report on real-world abilities, further reducing day-to-day performance variability.

Parents and caregivers of children with MPS IIIA report that sleep disturbances are common and severe [36], although sleep problems become less of an issue following disease or sleep medication regime progression. A recent report of parent experiences of the impact of MPS IIIA indicated that sleep not only impacts patients' lives, but also significantly impacts the lives of parents/caregivers [16]. In our natural history study, we did not find a clear overall trend in sleep improvement or worsening; we focused on the night waking subdomain of the CSHQ as it appeared to be most affected throughout the natural history of the disease compared with other subdomains. Our observations from the CSHQ showed that night wakings were prevalent, although they declined over time. However, the sleep quality of the patients in this trial was not compared with healthy controls, and it may be argued that night wakings naturally decrease with age. Given the prevalent use of sleep medication in MPS IIIA patients, it is important to consider whether sleep pattern data can be evaluated independently of medication usage data, and whether a reduction in sleep medication use could be a potential endpoint for clinical trials.

Pain is one of the most common symptoms reported by parents [16]. Given the complexity of identifying pain in children who are unable to communicate verbally, this symptom is often underestimated. However, using pain as a reliable endpoint for patient populations with severe cognitive and behavioral deficits remains complex. In healthy children, typical symptoms of pain are expressed when pain is experienced; however, these symptoms may be a result of the behavioral and emotional aspects of MPS IIIA, and may be misinterpreted by the parents/caregivers. Recurrent pain can have a significant effect on all aspects of daily life, including sleep and family interactions, and can lead to distress, anxiety, depression, irritability, insomnia, fatigue, and negative coping behaviors in the child [37]. We observed that the patients' pain score as measured with the ITQOL increased over time within the older population with a DQ <50. It is particularly challenging to identify the cause of pain, and appropriately manage it, in children with impaired and declining cognitive and communication faculties [37]. Therefore, although it is important that the parents/caregivers report that they are seeing pain in patients with MPS IIIA, it remains a challenging issue to address.

Finally, many parents/caregivers report challenges with feeding children with MPS IIIA throughout the disease course, and eating issues impact the health of the patient and the lives of the parents/caregivers [16]. We identified a cluster of questions (A, C, E, K) relating to eating in the VABS-II daily living questionnaire. Patients' scores in this study declined over time, signaling that eating may be another worthy endpoint for assessment in future studies.

As a prospective longitudinal analysis, this study adds important natural history data on the clinical course of MPS IIIA and the suitability and sensitivity of outcome measures to detect change in cognition and motor development. However, the study has some limitations. An important limitation is that age equivalent measures (i.e. DA) and DQ have previously been identified as being less than ideal for assessment of very young and older children, and are statistically problematic as the underlying standard score intervals are not equal [38,39]. However, at this time, DA/DQ are measures available for cognitive assessment and the limitations of this approach were partially addressed by examination of the raw BSID-III scores [40]. Another limitation of this study is that the relevant statistical analyses and clusters of questions used to analyze walking and eating were identified post hoc.

5. Conclusions

In conclusion, this multicenter, prospective observational study describes the natural history of MPS IIIA in a cohort of 23 patients with the severe form of MPS IIIA over a 2-year period and expands knowledge on the rate and impacts of cognitive decline and neurodegeneration over the disease course. All patients in our cohort started the study with severe early onset disease and a cognitive development level below normal for age. A progressive decrease in patients' DQ, speech and language skills, and motor/walking skills was seen during the 2-year observation period. A significant delay was seen between the decline in cognition and loss of motor skills/walking ability. In line with increasing recognition of the importance of patient and parent/caregiver outcome measures in clinical studies of MPS IIIA, we assessed sleep disturbance, pain, and eating issues among the cohort over time. No consistent pattern of sleep disturbance was found, although frequent night waking was common. Pain scores steadily increased over the duration of the study and eating scores declined over time, consistent with loss of motor function. Collectively, these data support the use of BSID-III score-derived cognitive scores as an endpoint with which to measure decline in cognitive ability in MPS IIIA patients and the suitability of VABS-II domain scores to assess change in language, and motor function over time. However, more sensitive measures may be required to examine changes in sleep patterns, pain, and QoL in this population, all of which may be confounded by the use of medications to manage the disease.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2021.12.002.

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