



A longitudinal study of emotional adjustment, quality of life and adaptive function in attenuated MPS II



Elsa G. Shapiro^{a,*}, Kyle Rudser^b, Alia Ahmed^a, Robert D. Steiner^{c,1}, Kathleen A. Delaney^{a,2}, Brianna Yund^{a,3}, Kelly King^a, Alicia Kunin-Batson^d, Julie Eisengart^a, Chester B. Whitley^a

^a Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

^b Division of Biostatistics, University of Minnesota, Minneapolis, MN, USA

^c Department of Pediatrics, Oregon Health & Science University, Portland, OR, USA

^d HealthPartners Institute, Minneapolis, MN, USA

ARTICLE INFO

Article history:

Received 8 March 2016

Accepted 24 March 2016

Available online 1 April 2016

Keywords:

Attenuated mucopolysaccharidosis type II

Behavioral outcomes

Quality of life

Adaptive functions

ABSTRACT

Objectives: The behavioral, adaptive and quality of life characteristics of attenuated mucopolysaccharidosis type II (MPS II) have not been well studied. Understanding changes over time in the attenuated phenotype may assist in helping achieve better outcomes in long-term function. This longitudinal study investigates these outcomes in relation to age, somatic disease burden, and IQ. Specifically, somatic disease burden is a major challenge for these patients, even with treatment with enzyme replacement therapy.

Methods: 15 patients, 10 between ages 6 and <12 and 5 between ages ≥12 and 18, were selected who had at least 2 yearly visits. The occurrence of physical signs, the Physical Symptom Score, and IQ in these two groups was studied as well as the longitudinal association of age with standardized measures of quality of life, adaptive function, and behavioral symptoms as rated by parents and the child's self-report. Slopes by age across and within patients were calculated for these measures.

Results: All but one child had hearing loss, most had joint contractures and short stature. Somatic disease burden increased with age. IQ, although normal for most, also improved with age in those under 12 years of age. Physical quality of life decreased while psychosocial quality of life increased with age. Although other adaptive skills were in the broad average range, daily living skills were low at baseline relative to normative data and decreased over time. Behavior ratings indicated improvement in attention and hyperactivity over time. No patient had severe psychopathology, but older children reported an increasing sense of inadequacy and low self-esteem on self-report, presumably due to increasing awareness of differences from peers over time.

Conclusions: Attenuated MPS II patients have increasing somatic disease burden and poor physical quality of life as they develop as well as decreasing self-esteem and sense of adequacy. Psychosocial quality of life, adaptive skills, and attention improve. Recognition of and intervention around these issues will be beneficial to MPS II attenuated patients who have the resources to use such assistance to improve their long-term outcomes.

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1. Introduction

This study investigates the emotional adjustment, quality of life, and adaptive function in attenuated mucopolysaccharidosis type II or Hunter syndrome patients, exploring patterns of adaptation and adjustment in relationship to age and somatic disease burden variables longitudinally. MPS II, a rare X-linked lysosomal disease with an incidence of 1

in 170,000 [1], results from absent or insufficient iduronate-2-sulfatase, resulting in a multisystem disease with progressive accumulation of glycosaminoglycans, namely heparan and dermatan sulfate, in many organs. Neurodegenerative disease is progressive in the severe form which affects most MPS II patients [2]. An attenuated form of MPS II (MPS II_{att}) affects about a fourth of patients [3] and generally has a normal course of cognitive development [4] without age-related decline. However, somatic disease burden which includes such symptoms as hearing loss, skeletal dysplasia, and cardiorespiratory problems appear to worsen with older age [4] in all MPS II patients. Enzyme replacement therapy has been recommended for all MPS II patients [2].

Recently we have reported that patients with MPSII_{att} have problems with attention that appear to be linked to lack of normal

* Corresponding author at: 820 NW 12th Ave, Portland, OR 97209, USA.

E-mail address: shapi004@umn.edu (E.G. Shapiro).

¹ Currently at University of Wisconsin, Madison, USA.

² Currently at Shapiro & Delaney LLC, USA.

³ Currently at University of Wisconsin, Milwaukee, USA.

development of white matter in the brain as well as somatic disease burden [4]. Along with our clinical observations of the adjustment and behavioral adaptation problems of MPS II_{att} patients during adolescence, we explore age, and disease burden over time in relationship to normative data on standardized measures of emotional/behavioral adjustment, adaptive skills (including communication, daily living skills and socialization), and quality of life.

Although the considerable behavioral abnormalities in the severe form of MPS II have been described, little literature could be found examining quality of life, adaptive behavior or psychological problems in MPS II_{att} patients, and of those describing them, precise characterization with standardized instruments often is lacking [5]. Furthermore, longitudinal data on these questions has not been heretofore presented. It is well known that the burden of disease and disability in MPS II_{att} is improved after enzyme replacement therapy but residual problems remain especially in children treated late [6,7,8]. Particular reference has been made to hearing loss, short stature, and physical disability as factors that may influence long-term life outcomes in MPS II_{att} despite relatively normal cognitive ability. Even if these problems are relatively mild, they may be obstacles in achieving life goals. Therefore, we examine the role of these disabilities and age in the development of psychological problems, adaptive behavior, and quality of life in MPS II_{att}.

2. Materials and methods

2.1. Subjects

Our patients were recruited from a pool of 25 patients who were enrolled in the multicenter longitudinal protocol NCT01870375 of the Lysosomal Disease Network (Longitudinal Studies of Brain Structure and Function). These patients are drawn from the same cohort as those in our previous report of attention and cognition [1] in MPS II. Inclusion criteria were 1) confirmed diagnosis of attenuated MPS II with an IQ > 70, 2) ability to cooperate with testing, 3) age at initial visit between 6 and 18, and 4) attended at least two visits. Of those not included, 1 younger child was dropped from the study for extreme behavior and noncooperation, 3 had only 1 data point, and 5 were over 18 years of age. We did not include those over age 18 as the measures we selected were not applicable to older patients and our goal was to investigate the role of children's age on changes in these variables. Each institution had IRB approval of the protocol, and consents and assents were obtained from study participants and caregivers at each local institution, which included permission to upload de-identified data to the RDCRN (Rare Disease Clinical Research Network) Data Monitoring and Coordination Center and to the University of Minnesota for analysis. All patients were receiving enzyme replacement therapy (ERT). Data were collected annually, beginning in October 2009 and completed in June 2014. Patients had between 2 and 4 visits depending on initial enrollment date.

2.2. Procedures

2.2.1. Demographic information

Socioeconomic status (SES) was determined by the Hollingshead two factor method using parental occupation and education [9].

2.2.2. Cognitive ability

IQ was measured on the Wechsler Abbreviated Scale of Intelligence (WASI) [10]. The WASI has high correlations with the longer versions of the Wechsler tests (0.87 with the Wechsler Intelligence Scale for Children-III and 0.97 with the Wechsler Adult Intelligence Scale-III) and minimizes fatigue in a half-day testing session [11].

2.2.3. Medical/treatment history

Detailed report of medical and treatment history was gathered by interview and medical record review. Somatic disease burden was calculated at each visit using the Physical Symptom Scale (PSS) [12]. PSS summary scores were based on skeletal/orthopedic, vision, hearing, and cardio-respiratory domains of the medical/treatment history report, as well as the number of surgical procedures and the presence of hydrocephalus. Each of the 6 PSS domains can be scored 0 to 3, which are then summed to form a total score that ranges from 0 to 18, with higher scores reflecting greater physical disease burden. In addition to the PSS score, age at symptom onset, age at MPS II diagnosis, and age at the time of ERT initiation and years of treatment were included. Information regarding dose and frequency of infusions was not available.

The frequency/percent of occurrence of a selection of physical symptoms (hearing impairment, use of hearing aids, short stature, joint contractures, and hydrocephalus) that may affect later adaptive and social-emotional development were calculated.

2.2.4. Behavioral measures

2.2.4.1. Adaptive behavior. All patients were assessed with the Vineland Adaptive Behavior Scales – Second Edition (VABS-II), a norm-referenced parent/caregiver report [13]. The VABS-II measures personal and social adaptation in the areas of communication, daily living skills, and socialization. The results rely on a concrete description of what the child typically does on a daily basis from a caregiver-completed questionnaire or standard interview. Scores are reported as standard scores with a mean of 100 and a standard deviation of 15. Higher scores reflect better adaptive functions.

2.2.4.2. Quality of life. The Child Health Questionnaire (CHQ) [14] is a 50-item parent-report survey of quality of life (QOL) for children age 5 to 18. It has established reliability and validity and is commonly used in children with chronic illness to measure children's physical and psychosocial well-being. We report here the summary measures of those two areas; Physical (CHQ-PhS) and Psychosocial (CHQ-PSS) respectively. The scores are norm-referenced T-scores with a mean of 50 and a standard deviation of 10. Higher scores reflect better quality of life.

2.2.4.3. Personality and behavior. The Behavior Assessment System for Children-Second Edition [15] includes standardized generic questionnaires that evaluate the psychological adjustment and self-perceptions of children. They include both clinical scales of emotional adjustment and adaptive behaviors. We have used the PRS, the parent rating scales, appropriate for our sample of children 5 to 18, and the SRP, the self-report of personality, usable from ages 8 to 18. For children ages 6 and 7, an interview based self-report was given. For both the parent report and self-report, scores are reported as T-scores with a mean of 50 and a standard deviation of 10. Higher scores are more abnormal except for adaptive scales where higher scores are better.

As there are many scales on the BASC-2, the following scales were selected for analysis from the PRS based on clinical observations and prior findings: depression, withdrawal, attention problems and adaptive skills. The following SRP scales were chosen based on clinical observations and parental report: social stress, anxiety, depression, locus of control, and sense of inadequacy. SRP adaptive scales that were included were interpersonal relationships, relations with parents, self-esteem and self-reliance. On the SRP for those over 8, attention problems and hyperactivity are reported. In addition to slopes over time, the percent of participants scoring outside the normal range will be reported.

2.3. Data categories

We divided our MPS II_{att} patients by age and by PSS score. Our clinical observations were that the developmental challenges occurring during and after puberty might affect social emotional outcomes. For the age groupings, we divided the group into those under 12 and those who had reached adolescence and were 12 and over. We conducted both cross sectional and longitudinal analyses for these two groups.

For the PSS score, we divided the group into those whose scores were <9 and those who had scores ≥9 (the midpoint). We examined the PSS scores at baseline in relation to behavioral outcomes.

2.4. Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Minnesota [16]. Descriptive statistics were tabulated with mean and standard deviation for continuous variables and frequency for categorical variables. Marginal associations across individuals were estimated using generalized

estimating equations and robust standard errors for confidence intervals and P-values. Conditional slopes representing within individual changes were estimated using linear mixed models with random intercept and model-based standard errors for confidence intervals and P-values. All analyses were conducted using R v3.1.1 [17].

3. Results

3.1. Demographic information

To assess socioeconomic status (SES), the Hollingshead 2 factor index based on occupation and education indicated that 7 children came from the highest SES category I; 2 children came from families in category II, 4 in category III, and 2 in category IV. No families were in the lowest SES group. 10 of 15 children's parents had a college degree. There were two sets of full siblings and one set of half siblings.

Other demographic information as well as means and standard deviations for all measures are in Table 1.

Table 1
Patient descriptives: values are mean (sd) or N (%) where indicated. Values represent measurements from baseline (second visit for all except first for one participant). Age split at 12 and PSS score at 9. Because medical symptoms are part of the PSS score, only means by age were calculated.

Covariate	MPS II (N = 15)	Age < 12 (N = 10)	Age ≥ 12 (N = 5)	PSS < 9 (N = 9)	PSS ≥ 9 (N = 6)
Age (years)	10.84 (3.09)	9.20 (1.93)	14.11 (2.22)	9.75 (3.02)	12.47 (2.61)
IQ	103 (15.57)	104 (13.84)	100 (20.15)	108 (10.65)	94.67 (19.34)
PSS	7.93 (1.49)	7.40 (1.43)	9.00 (1.00)	7.00 (1.12)	9.33 (0.52)
Number of patients with hearing loss	14 (93%)	9 (90%)	5 (100%)	–	–
Number of patients using hearing aids	10 (67%)	6 (60%)	4 (80%)	–	–
Number of patients with short stature	8 (53%)	4 (40%)	4 (80%)	–	–
Number with joint contractures	14 (93%)	9 (90%)	5 (100%)	–	–
Number with hydrocephalus	3 (20%)	2 (20%)	1 (20%)	–	–
Age at first ERT treatment	7.11 (3.27)	5.65 (2.69)	10.03 (2.07)	–	–
Years of ERT treatment	3.73 (1.88)	3.55 (1.95)	4.10 (1.07)	–	–
CHQ (T score) ^a					
– Missing CHQ	4 (26.67%)	4 (40.00%)	0 (0.00%)	2 (22.22%)	2 (33.33%)
– Psychosocial summary score	49.52 (10.95)	45.99 (12.93)	53.74 (7.07)	53.55 (8.08)	42.45 (12.84)
– Physical summary score	35.76 (17.86)	43.45 (9.45)	26.53 (22.15)	43.15 (10.74)	22.82 (21.95)
VABS-II (none missing) (standard score) ^a					
– Composite	98.40 (14.57)	98.60 (13.41)	98.00 (18.38)	105 (12.78)	88.67 (11.98)
– Daily living skills	95.27 (16.26)	97.40 (16.50)	91.00 (16.69)	102 (15.09)	85.33 (13.37)
– Communication	100 (15.67)	98.00 (13.84)	105 (19.63)	105 (12.39)	92.83 (18.09)
– Socialization	102 (13.85)	104 (12.92)	98.40 (16.53)	108 (12.64)	92.67 (10.60)
BASC-P: parent report (none missing) (T score) ^a					
– Depression	53.47 (12.61)	53.90 (13.84)	52.60 (11.15)	47.11 (7.79)	63.00 (12.90)
– Withdrawal T-score	56.53 (14.74)	54.80 (16.36)	60.00 (11.64)	47.67 (8.17)	69.83 (12.16)
– Attention problems T-score	49.27 (9.15)	51.00 (10.37)	45.80 (5.36)	49.56 (10.03)	48.83 (8.57)
– Adaptive skills T-score	48.20 (8.48)	47.00 (8.81)	50.60 (8.14)	51.00 (7.92)	44.00 (8.10)
BASC: self-report (T-score) ^a					
Clinical scales (higher scores are more abnormal)					
– Missing values for scales below	3 (20.00%)	2 (20.00%)	1 (20.00%)	3 (33.33%)	0 (0.00%)
– Social stress T-score	47.08 (9.09)	48.50 (9.70)	44.25 (8.22)	41.83 (5.91)	52.33 (8.98)
– Anxiety T-score	49.08 (8.17)	48.00 (8.86)	51.25 (7.23)	43.00 (4.38)	55.17 (6.24)
– Depression T-score	45.54 (4.33)	47.25 (4.59)	42.80 (2.05)	43.71 (2.06)	47.67 (5.47)
– Missing values for scales below	4 (26.67%)	3 (30.00%)	1 (20.00%)	4 (44.44%)	0 (0.00%)
– Locus of control T-score ≥ 8 ^b	46.91 (9.43)	48.86 (9.65)	43.50 (9.26)	42.40 (5.50)	50.67 (10.78)
– Sense of inadequacy T-score ≥ 8	50.09 (6.67)	49.29 (5.94)	51.50 (8.58)	46.60 (5.64)	53.00 (6.42)
– Attention problems T-score ≥ 8	49.36 (10.29)	52.29 (11.48)	44.25 (5.85)	48.20 (9.26)	50.33 (11.86)
– Hyperactivity T-score ≥ 8	50.45 (7.53)	50.14 (8.32)	51.00 (7.07)	46.40 (6.84)	53.83 (6.77)
Adaptive scales (higher scores are better)					
– Missing values for scales below	3 (20.00%)	2 (20.00%)	1 (20.00%)	3 (33.33%)	0 (0.00%)
– Interpersonal relations T-score	51.00 (11.31)	48.62 (12.68)	55.75 (6.95)	55.50 (7.20)	46.50 (13.44)
– Self-esteem T-score ≥ 8	53.83 (5.57)	51.29 (4.75)	57.40 (4.93)	54.50 (4.93)	53.17 (6.55)
– Missing values for scale below	4 (26.67%)	3 (30.00%)	1 (20.00%)	4 (44.44%)	0 (0.00%)
– Relations with parents T-score ≥ 8	51.82 (10.00)	48.00 (8.89)	58.50 (9.04)	47.40 (9.32)	55.50 (9.73)
– Missing values for scale below	5 (33.33%)	4 (40.00%)	1 (20.00%)	4 (44.44%)	1 (16.67%)
– Self-reliance T-score ≥ 8	50.60 (14.60)	45.17 (13.88)	58.75 (13.07)	50.20 (12.87)	51.00 (17.71)

^a T score (mean 50, standard deviation 10); standard score (mean 100, standard deviation 15).

^b For items marked > 8, item is not give under age 8.

3.2. Cognitive ability

IQ was found to be in the average range for our MPS II sample, consistent with the socioeconomic level of this group.

3.3. Medical status

The PSS score [8] reflects a significant disease burden with medical problems arising in many organ systems especially in the older group. For individual medical items, all but one patient had hearing loss and two-thirds wore hearing aids. Also, all but one patient had joint contractures. Short stature was reported in 8 patients in the entire group, but it primarily was reported in 4 of 5 older participants. Of the entire group, three patients had hydrocephalus; two of them had shunts.

All children were on ERT. The range of years on treatment was from 0.30 to 6.56 with a mean of 3.73 years. Only one patient had less than one year of treatment. No adverse events around ERT treatment were reported.

3.4. Behavioral measures

While the CHQ-PSS (Psychosocial) score was within the average range, the CHQ-PhS (Physical score) was >2 standard deviations below the normative average in the older children and 1.5 standard deviations below average for the entire group, indicating the impact of physical disability on health-related QOL (HR-QOL). Similarly for those

with a PSS score of 9 or above, the CHQ-PhS score was >2 standard deviations below the mean.

All VABS-II Scores indicate that adaptive skills were within the average range when examining both the younger and older groups. However, in the group with PSS scores of ≥9, Daily Living Skills were a standard deviation below the mean compared to those with scores <9 who were average.

Mean scores are within the average range on the BASC-2-PRS with the exception of the withdrawal score in the older children which was one standard deviation above the mean (in the abnormal direction). On the BASC-2-SRP, children do not report themselves as outside the normal range on any scales. For those with a PSS score of ≥9, parents report more depression and withdrawal and children self-report more anxiety compared to those with scores <9.

Missing data is reported for each test. We had some missing data for the BASC2-SRP and for the CHQ as noted in Table 1.

3.4.1. Slopes across and within subjects by age

Dividing the group into a younger (<12) and older (≥12) cohort, slopes were calculated both across and within individuals per year in age and can be found in Tables 2 and 3.

Significant association of age with increasing somatic disease burden across individuals was found over time. IQ appears to increase within individuals especially in the younger group.

For the CHQ across individuals the CHQ-PhS worsens with age but the change does not achieve significance. However, within individuals across the entire group, a trend of worsening was seen (P = 0.065).

Table 2
Marginal slope *across individuals* per year in age.

Score	All (N = 15)		Age < 12 (N = 10)		Age ≥ 12 (N = 5)	
	Estimate (95% CI)	(N = 6)	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
PSS ^a	0.29 (0.17, 0.42)	<0.001	0.39 (0.22, 0.56)	<0.001	0.06 (−0.30, 0.42)	0.729
WASI-IQ ^b	−0.88 (−2.86, 1.09)	0.382	0.24 (−3.26, 3.74)	0.892	−3.12 (−7.79, 1.54)	0.190
CHQ ^b						
CHQ: PSS ^b	0.77 (−0.40, 1.94)	0.195	2.42 (0.79, 4.04)	0.004	−0.50 (−3.23, 2.23)	0.720
CHQ: PhS ^b	−1.86 (−4.21, 0.50)	0.122	−1.77 (−3.82, 0.28)	0.091	−2.68 (−10.52, 5.16)	0.503
VABS-II ^b						
VABS-II: composite ^b	−0.58 (−1.97, 0.81)	0.414	0.07 (−2.25, 2.40)	0.951	−1.09 (−5.61, 3.43)	0.636
VABS-II: DLS ^b	−1.85 (−3.16, −0.54)	0.006	−1.61 (−3.77, 0.56)	0.147	−1.73 (−6.16, 2.69)	0.443
VABS-II: communication ^b	0.10 (−1.50, 1.70)	0.904	−0.46 (−2.95, 2.02)	0.714	0.59 (−3.92, 5.10)	0.797
VABS-II: socialization ^b	−0.51 (−1.83, 0.81)	0.450	0.02 (−2.18, 2.22)	0.988	−0.59 (−4.84, 3.65)	0.784
BASC PR clinical scales ^a						
BASC PR: depression ^a	−0.03 (−1.36, 1.30)	0.964	−0.17 (−2.97, 2.63)	0.905	−0.74 (−3.30, 1.82)	0.569
BASC PR: withdrawal ^a	0.82 (−0.68, 2.32)	0.282	2.03 (−0.05, 4.11)	0.056	−2.63 (−7.04, 1.79)	0.243
BASC PR: attention ^a	−1.03 (−1.79, −0.28)	0.007	−1.33 (−2.79, 0.12)	0.072	−0.39 (−2.13, 1.36)	0.663
BASC PR adaptive scale ^b						
BASC PR: adaptive ^b	0.77 (−0.35, 1.90)	0.177	0.50 (−0.76, 1.76)	0.439	1.19 (−2.52, 4.89)	0.530
BASC SR clinical scales ^a						
BASC SR: social stress	−0.74 (−2.01, 0.52)	0.248	−0.86 (−4.52, 2.81)	0.647	−0.03 (−2.18, 2.12)	0.980
BASC SR: anxiety	0.53 (−0.47, 1.54)	0.299	0.46 (−2.39, 3.30)	0.754	1.67 (−0.12, 3.47)	0.068
BASC SR: depression	−0.94 (−1.88, 0.01)	0.051	−1.42 (−4.47, 1.63)	0.361	0.03 (−0.56, 0.61)	0.932
BASC SR: locus of control	−0.97 (−2.03, 0.09)	0.074	−1.65 (−4.90, 1.60)	0.319	0.26 (−1.14, 1.65)	0.715
BASC SR: sense of inadequacy	0.99 (−0.34, 2.33)	0.146	−0.48 (−2.99, 2.03)	0.708	3.23 (1.10, 5.35)	0.003
BASC SR: attention problems	−0.97 (−2.26, 0.32)	0.141	−2.87 (−6.09, 0.35)	0.081	0.76 (−1.86, 3.38)	0.569
BASC SR: hyperactivity	−0.56 (−2.22, 1.09)	0.504	−3.43 (−5.70, −1.17)	0.003	1.62 (−0.31, 3.56)	0.100
BASC SR adaptive scales ^b						
BASC SR: interpersonal relations	1.23 (−0.07, 2.53)	0.065	1.09 (−2.51, 4.68)	0.554	0.85 (−0.66, 2.37)	0.269
BASC SR: relations with parents	1.81 (0.46, 3.16)	0.009	3.24 (0.44, 6.04)	0.023	0.94 (−1.63, 3.52)	0.472
BASC SR: self-esteem	0.30 (−0.75, 1.35)	0.580	0.20 (−2.01, 2.41)	0.862	−1.21 (−3.49, 1.07)	0.297
BASC SR: self-reliance	1.69 (−0.37, 3.75)	0.109	5.04 (0.20, 9.88)	0.041	0.91 (−2.60, 4.41)	0.612

^a Lower scores are better.
^b Higher scores are better.

Table 3
Conditional slope *within individuals* per year in age.

Score	All (N = 15)		Age < 12 (N = 10)		Age ≥ 12 (N = 5)	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
PSS ^a	0.00 (0.00, 0.00)	1.000	0.00 (0.00, 0.00)	1.000	0.00 (0.00, 0.00)	1.000
WASI-IQ ^b	2.31 (0.92, 3.71)	0.001	3.72 (1.45, 5.99)	0.001	1.04 (−0.90, 2.98)	0.292
CHQ ^b						
CHQ: PSS ^b	1.06 (−0.23, 2.35)	0.109	2.41 (−0.03, 4.85)	0.053	1.48 (−0.69, 3.66)	0.181
CHQ: PhS ^b	−1.75 (−3.62, 0.11)	0.065	−1.79 (−4.22, 0.64)	0.148	2.62 (−1.61, 6.85)	0.224
VABS-II ^b						
VABS-II: composite ^b	0.29 (−1.17, 1.76)	0.694	0.50 (−1.94, 2.94)	0.690	0.43 (−2.92, 3.77)	0.803
VABS-II: DLS ^b	−0.78 (−2.39, 0.82)	0.339	−1.13 (−4.23, 1.98)	0.477	0.67 (−1.67, 3.02)	0.574
VABS-II: communication ^b	1.31 (−0.13, 2.76)	0.075	0.68 (−1.56, 2.91)	0.553	2.37 (−0.69, 5.42)	0.129
VABS-II: socialization ^b	−0.42 (−1.86, 1.02)	0.567	−0.01 (−2.40, 2.37)	0.991	−0.36 (−4.56, 3.84)	0.867
BASC PR clinical scales ^a						
BASC PR: depression ^a	−0.80 (−1.85, 0.25)	0.134	−1.33 (−3.30, 0.65)	0.188	−2.11 (−3.63, −0.59)	0.006
BASC PR: withdrawal ^a	0.26 (−1.29, 1.82)	0.741	−0.05 (−3.04, 2.93)	0.971	−1.94 (−4.44, 0.55)	0.127
BASC PR: attention ^a	−1.02 (−1.93, −0.11)	0.028	−1.79 (−3.60, 0.03)	0.053	−1.46 (−2.64, −0.29)	0.014
BASC PR adaptive scale ^b						
BASC PR: adaptive ^b	0.97 (0.08, 1.86)	0.033	1.09 (−0.47, 2.65)	0.172	2.11 (0.41, 3.81)	0.015
BASC SR clinical scales ^a						
BASC SR: social stress	−0.93 (−2.10, 0.24)	0.118	−1.40 (−4.42, 1.61)	0.361	−0.12 (−1.94, 1.70)	0.894
BASC SR: anxiety	0.07 (−1.01, 1.15)	0.903	−0.97 (−3.29, 1.34)	0.410	1.28 (−0.47, 3.03)	0.153
BASC SR: depression	−1.34 (−2.21, −0.46)	0.003	−1.87 (−4.16, 0.42)	0.110	0.03 (−0.63, 0.68)	0.939
BASC SR: locus of control	−1.49 (−2.54, −0.43)	0.006	−2.11 (−3.93, −0.29)	0.023	−0.21 (−2.03, 1.62)	0.823
BASC SR: sense of inadequacy	0.76 (−0.33, 1.84)	0.170	−0.41 (−3.18, 2.36)	0.771	2.58 (0.67, 4.48)	0.008
BASC SR: attention problems	−1.01 (−2.41, 0.40)	0.160	−2.02 (−6.54, 2.51)	0.383	0.25 (−1.42, 1.93)	0.767
BASC SR: hyperactivity	−1.09 (−2.20, 0.01)	0.053	−2.52 (−5.40, 0.36)	0.086	0.04 (−1.86, 1.94)	0.969
BASC SR adaptive scales ^b						
BASC SR: interpersonal relations	1.49 (0.21, 2.76)	0.022	1.77 (−1.55, 5.09)	0.296	1.17 (0.30, 2.05)	0.009
BASC SR: relations with parents	1.60 (0.43, 2.76)	0.007	2.06 (−1.01, 5.14)	0.188	1.18 (−1.01, 3.38)	0.291
BASC SR: self-esteem	0.47 (−0.41, 1.36)	0.294	0.90 (−1.10, 2.89)	0.378	−1.90 (−3.06, −0.73)	0.001
BASC SR: self-reliance	1.27 (−0.08, 2.62)	0.064	4.46 (1.40, 7.51)	0.004	0.17 (−1.80, 2.13)	0.869

^a Lower scores are better.

^b Higher scores are better.

Both across and within individuals the CHQ-PSS quality of life improves over time.

On the VABS-II, across all individuals the Daily Living Skills domain significantly decreases with age. This change was not detected on within-individual slopes. Changes were not observed in communication or socialization.

For the BASC-PRS, across individuals, a worsening of withdrawal symptoms in younger children was noted. However, within each individual, improvement with time was noted for symptoms of depression and poor attention and in adaptive skills, such that in older children, adaptive skills improve and depression lessens.

The BASC-2-SRP was consistent with parent report; decreasing inattention, hyperactivity, and depression with age. However, within the patients 12 and over, an increasing sense of inadequacy and anxiety, and decreased self-esteem were reported over time.

3.4.2. Frequency of scores outside the average range

In the context of relatively normal psychological adjustment for the entire group, several individual patients' scores were not in the average range. The rate of parent and self-reported problems was determined by calculating the frequency of patients' scores on each scale that was greater than a standard deviation from the mean, indicating concern but not in the clinically significant range. For the BASC-PRS scales, 10 or 59% demonstrated elevated scores for at least one visit on the withdrawal scale and 6 (35%) on the depression scale. Only 3 (18%) of 16 were described as inattentive by their parents. Consistent elevations from year to year were also calculated with 6 (38%) parent reports

showing elevated withdrawal scores on 2 or more visits. Parent ratings that fell in the clinical range, more than two standard deviations above the mean, were found for five patients but of those, only three were consistently at that level over two or more visits.

BASC-SRP results were more variable. The most frequent scales at least a standard deviation above the mean were attention and hyperactivity scales; 4 of 13 describing problems with attention and hyperactivity. 4 (29%) described themselves as low on interpersonal relations. However, in no case were they consistent over time. Only one patient had scores that were over 2 standard deviations (in the clinical range); rather, of those with elevations most were in the 60–70 range indicating moderate concerns.

4. Discussion

Mucopolysaccharidosis type II (MPS II) is an X-linked recessive lysosomal disorder with a spectrum of severity from the severe neurodegenerative form to an attenuated form with less neurological abnormality. The behavioral and adaptive aspects of the severe form have been better characterized than attenuated MPS II [1–3,18–20]. The neurological abnormality in MPS II diverges in the two groups and clearly those with CNS abnormality have progressive cognitive decline and well-documented disruptive behavior [20].

The behavioral and social-emotional characteristics in the attenuated form of MPS II have not been well characterized. This study extends observations to longitudinal examination of the effect of age on behavior, adjustment, and quality of life of patients between age 6 and 18 with

the attenuated form of MPS II, as well as the patterns of somatic disease burden and IQ. Our previous research has described normal intellectual ability, but below average attention span on a computerized measure of attention associated with abnormal development of corpus callosum and white matter volumes [4]. Other imaging studies have found that MRIs in attenuated patients are abnormal but generally stable and consist of enlarged Virchow Robin spaces, enlarged ventricles and white matter abnormalities [21–25]. Progression on neuroimaging was found mainly in the severe phenotype except for hydrocephalus which did occur in attenuated patients even with ERT treatment, as we have observed in 20% of our sample.

While not the primary objective of this study, IQ was measured across individuals and within individuals longitudinally. No significant effects were found across individuals, replicating previous findings [4]. However, the younger <12 year group showed significant increase per year in IQ scores within individual subjects. The effect size was 3.72 points per year. This increase was not seen in the ≥12 year group. The reason for this is not immediately apparent, although it may be due either to brain maturation or possibly to environmental enrichment, given the advantages that may be associated with the high SES of this sample. This finding needs to be replicated with a larger and more economically diverse group.

Somatic burden of disease is severe for most patients irrespective of their central nervous system (CNS) involvement. We have found that hearing loss as previously described [2,26] is nearly universal. Short stature and joint contractures occur in most patients and appear to worsen with age [1,2,27]. Hydrocephalus occurs in 20% of attenuated patients; perhaps less than in severe patients, but nevertheless a considerable risk for these patients.

Using our recently developed overall score of somatic disease burden (PSS) [12], a score of 7.93 in this MPS II_{att} group was almost identical to our previous report of MPS I attenuated patients PSS score (7.89) for a group of similar age range [28]. Means for Daily Living Skills for those with PSS scores ≥9 differ by one standard deviation from those with lower scores, suggesting an impact of physical disease burden on activities of daily living. Examining slopes across age groups, the PSS increased with age and, Daily Living Skills, despite being in the average range on the VABS-II, decreased significantly with age. This differs from Kato's finding of normal progression with age [29] in activities of daily living using the FIM (Functional Independence Measure) in MPS II_{att}. This may be due to differences in what these two scales measure.

While the somatic disease burden may be comparable to attenuated MPS I, in contrast MPS II_{att} IQs are quite a bit higher than expected and contrast with lower IQ scores (mean = 91.1, s.d. = 17.2) in the attenuated MPS I of the same age [30]. We noted the robust IQ performance of these patients before [4], but have determined in this study that a likely explanation is the socioeconomic status of this sample. Recruitment of such a high SES group results from the willingness to participate in a non-treatment study requiring some resources. While transportation and expenses were provided for our patients, it nevertheless requires resources to travel and participate in a longitudinal study that does not provide treatment. To counter the lack of benefit, we provided feedback to parents regarding results, and established a positive relationship with most of the families who came to our center. Given the higher than average SES, provision of therapies and specialized services, as well as more intense medical care should also be considered as possible reasons for the relatively positive psychosocial outcomes of these patients. Thus, we would caution that the outcomes for the patients in this study should be considered optimum.

Two of 15 (13%) were cognitively below the average range (defined as IQs <85) in the attenuated group comparable to 11.3% in Schwartz et al.'s report [31] of a Brazilian MPS II_{att} group.

Overall we found that patients with MPS II_{att} report a physical quality of life that declines over time but that their psychosocial quality of life improves. Lower physical QOL has been described before, but in patients who were pre-ERT treatment and at one time point [32]. The

patients in our sample were all treated for a mean of 3.73 years prior to this study. Similar to our sample, in the Needham et al. [33] study of HR-QOL, physical health was worse than psychosocial health with a considerable difference from the norm. Our patients were within the average range for psychosocial QOL and considerably below average on physical quality of life with those at or over 12 years of age or those who had a PSS score ≥ 9, being on average 2.5 standard deviations below the mean; these findings are consistent with Needham et al.'s results [33]. Given that four children had missing CHQ's, and that they were all in the under 12 group, these QOL results should be applied only to those in the 12 and over group.

Both of these findings are borne out by results from other measures. On the VABS-II, while daily living skills scores decline with advancing age, socialization and communication improve normally. This may be explained by their intact IQ and the development of coping skills (measured by the socialization domain on the VABS-II) and adaptation over time that enables these children to deal with interpersonal issues even as physical problems persist and/or worsen. However, the physical disease burden progressively impacts their independence in activities of daily living. This finding was corroborated by the work of Needham et al. [34] who found overall lower scores on the VABS-II, but a similar pattern of relatively lower Daily Living Skills than either Communication or Socialization in a cross sectional sample.

With regard to emotional difficulties, this appears to be the first report of social emotional behavioral functioning in MPS II_{att}. These children are doing better than expected based on their disease history. Overall, they appear to report decreased behavioral manifestations of attention difficulties and hyperactivity with time, and no serious psychopathology unlike a subset of the MPS I group [35]. However, in the older patients, increasing sense of inadequacy and low self-esteem suggest growing awareness of differences as they mature and possibly their inability to engage in daily living skills tasks as independently as their peers. In addition, as MPS II is an X-linked disorder, and thus exists in males, it is important to consider the probable effect of physical limitations on self-esteem in a population that has been socialized to play sports to develop relationships or achieve social status [36–37]. A strong association has been found between sports participation and self-image and psychological well-being [38] with a possible negative impact on self-image among students who are not skilled at sports, [39] although perceived competence seems to have a greater impact than actual ability [40]. These results are based on the BASC-PR, a more sensitive measure than the BASC-SR.

A note of caution regarding the BASC-SR; our younger patients often struggled to complete the self-report, thus there are missing values in the <12 group. Moreover, scores on the BASC-SR even in the older patients were mostly in the average range, and often discrepant from parent ratings. Also, the lack of consistency from year to year was more than expected. There is a great need for a better, more sensitive, and perhaps disease-specific self-report measure of social emotional functioning for children with MPS diseases.

But given the good psychosocial quality of life and adaptive behavior (other than daily living skills which are likely impacted by problems with physical functioning), children with MPS II_{att} appear to have an increasing ability to psychologically cope with their disabilities as well as benefit from counseling around improving their sense of efficacy. The positive social milieu for these patients has likely improved their coping with the disease state given that both of these factors, disease state and social environment, contribute to the behavioral phenotype [41]. However, the increasing sense of inadequacy and low self-esteem do place MPS II_{att} individuals at risk for depression as they move into adulthood. Six of the 15 patients demonstrated outside the normal range scores on withdrawal and depression.

In conclusion, patients with MPS II_{att} have significant physical disability that worsens with age and causes a poor physical quality of life despite ERT and adequate cognitive skills. The commonly used term 'attenuated' does not adequately describe the somatic burden of these

patients who progressively become more disabled physically. Even the term non-neurological is not accurate as these children often have very abnormal MRIs, show an abnormal development of white matter, and are at risk for both cord compression and hydrocephalus [2,4].

In contrast, good coping, communication and social skills, have led to a better than expected psychosocial quality-of-life. However, a limitation of this study is the small number of subjects and the high SES in the sample. Although MPS II_{att} patients are not common, a larger international study could clarify whether improved psychosocial quality of life is a function of intervention efforts of this high socioeconomic status sample or a common finding. Another limitation of this study is our lack of detailed information regarding ERT (e.g. dosing regimen, tolerance of infusions and frequency of infusions) and the variability in duration of ERT across our patients (ranging from <1 year to 6.56 years of treatment), resulting in differential exposure to ERT across the sample. Given this variability and our small sample size, we were not able to examine the role of ERT in children's quality of life or emotional-behavioral/adaptive outcomes.

Behaviorally, problems with attention and activity level appear to improve in these children, but a sense of inadequacy and low self-esteem seem to emerge as children become more physically incapacitated but at the same time more self-aware and compare themselves with other children. Early intervention to promote self-esteem and a sense of competency may help to overcome some of these problems. Their constellation of strong IQ and functional communication skills make them candidates for good outcomes with rehabilitation therapies and counseling focusing on self-efficacy. These findings may provide guidance for understanding the natural history of the psychological aspects of this disease and possible prevention of later more serious psychological adjustment problems.

Funding sources

- The Lysosomal Disease Network supported this study through “Longitudinal Studies of Brain Structure and Function in the Mucopolysaccharidoses” 2009–2014 (E. Shapiro, P.I.). The Lysosomal Disease Network (U54NS065768) is a part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network, supported through collaboration between the NIH Office of Rare Diseases Research at the National Center for Advancing Translational Science, the National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH (C. Whitley P.I.).
- Shire (CON00000026631) supported this study as an investigator initiated research grant—(P.I. E. Shapiro) Shire was given the opportunity to review this manuscript, but the opinions and conclusions remain those of the authors.
- This project was supported in part (K. Rudser) by the National Center for Advancing Translational Sciences, National Institutes of Health, through University of Minnesota—CTSI Grant Number NCATS UL1TR000114. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Acknowledgments

We are very grateful for the cooperation of our participants. We thank Brenda Diethelm-Okita, David Erickson, and Evelyn Redtree in the Lysosomal Disease Network office at the University of Minnesota for administrative assistance. We are also grateful to the Center for Neurobehavioral Development for the provision of infrastructure for this research.

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