The Psychosocial Impact of Fabry Disease on Pediatric Patients

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Abstract

Keywords

- Fabry disease
- pediatric
- psychosocial functioning
- inborn error of metabolism

Fabry disease (FD) is a multisystemic disease that has previously been reported to result in poorer quality of life and psychosocial functioning in impacted adults. However, prior to the current study, limited data were available on the impact of FD in children and adolescents. Therefore, the present study examined the differences of quality of life, psychosocial functioning, and depression in children with FD as compared with a healthy sample. Results indicated that children with FD were experiencing poorer quality of life than their healthy counterparts. Notably, results consistently identified adolescents with FD as more heavily impacted than younger children, although not to the same degree as adults with FD as reported in previous studies. Therefore, adolescence may be a critical point in the development of individuals with FD during which effective multidisciplinary interventions could be utilized to prevent poor quality of life and psychosocial functioning in adulthood.

Introduction

Fabry disease (FD) is a rare, panethnic, X-linked lysosomal storage disorder that affects between 1 in 40,000 and 1 in 117,000 individuals.^{1,2} A deficiency of the enzyme α -galactosidase A (α -GAL) results in the progressive accumulation of globotriaosylceramide or Gb3.³ This results in a multisystemic disease affecting the renal, cardiac, pulmonary, ocular, and dermal systems, as well as the peripheral and central nervous systems.^{4–6} Few studies have examined the quality of life (QoL) and psychosocial functioning of pediatric patients with FD.

FD has been shown to have clinical consequences in children as young as 2 years old with increasing severity as one ages.³ Symptoms include decreased sweating and gastrointestinal (GI) pain.⁷ Additional symptoms in children and adolescents, particularly in males, affected by FD can include acroparesthesia, angiokeratomas, hypohidrosis GI symptoms, ocular findings, and poor heat and exercise tolerance.⁸ Early-childhood diagnosis is becoming more common for some

variants of FD due to the implementation of newborn screening.⁹

Currently, FD is understood and diagnosed as a broad range of phenotypes, ranging from the classical childhood presentation to the recently defined late-onset variety, formerly identified by its primary cardiac and renal involvement.^{10,11} Phenotype expression is also highly variable dependent on sex, as impacted hemizygous men classically present with more severe symptoms as opposed to heterozygous women, whose symptoms may range from nonclinical to severe.¹²

Although depression and poor QoL are prevalent among those with chronic illness and chronic pain, these areas have been relatively understudied in both children and adults with FD.¹³ Psychosocial difficulties for children with FD may include frequent school absences, poor participation in physical activity, and behavioral problems mostly related to chronic pain and GI symptoms.¹⁴ One study indicated that 80.9% of patients with FD responded that it has negatively impacted their ability to attend school and 83% of patients

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indicated that FD had affected their ability to participate in sports and physical activities.¹⁵

Similar to children with other chronic illnesses, children with FD also present with pain, fatigue, and GI features. Thus as might be expected according to the diathesis-stress model of depression, children with FD may also present with anxiety, depression, and decreased QoL.¹⁶ However, children with FD are unique; clinical manifestations are often diagnosed in late childhood and manifestations involve more than one organ. Thus, they may present with a wider variety of or more significant psychosocial deficits. To date, there have been no comprehensive studies examining the psychosocial functioning and health-related QoL of pediatric patients with FD. This study aimed to measure the psychosocial impact on children living with FD. Additionally, comparisons were made between children on enzyme replacement therapy (ERT) and those who were not.

Methods

The psychosocial functioning of participants was investigated using a quasiexperimental design. The study was reviewed and approved by the Institutional Review Board of the Pacific Graduate School of Psychology at Palo Alto University.

Participants and Procedures

The participants included English-speaking pediatric patients with FD and their parents. Patients were recruited from a conference for the National Fabry Disease Foundation in (September, 2011). Families signed assent and consent forms, and age-appropriate measures were distributed in person or by mail. Families of children with FD included at least one affected child (hemizygous affected male or heterozygous carrier female) and at least one parent with an FD-positive genotype, although the parent completing the survey was not FD in all cases. A total of 24 pediatric patients (10 males, 14 females) with FD, aged 6 to 18, and their parents participated. Seven children (5 males, 2 females) were on ERT at the time of the study and 13 (2 males, 11 females) were not on ERT.

Description of Assessment Measures

Pediatric Quality-of-Life Inventory 4.0. The Pediatric Quality-of-Life Inventory 4.0 (PedsQL) is a 23-item self- and parent-proxy report measuring health-related QoL.¹⁷ The PedsQL contains four scales: physical, emotional, social, and school functioning. This measure allows for comparisons to children with other chronic health conditions as well as healthy children. The PedsQL has strong validity for children with chronic illnesses, and acceptable reliability for the Total Scale Score ($\alpha = 0.88$ child, 0.90 parent report), Physical Health Summary Score ($\alpha = 0.80$ child, 0.88 parent), and Psychosocial Health Summary Score ($\alpha = 0.83$ child, 0.86 parent).¹⁸

Behavior Assessment Scale for Children, Second Edition.

The Behavior Assessment Scale for Children, Second Edition (BASC-2) measures adaptive and maladaptive functioning in emotional and behavioral domains.¹⁹ This measure is comprises 160 items and parents rank questions ("never occurs" to "almost always occurs") describing child behavior. The

Externalizing Problems Composite scale measures hyperactivity, aggression, and conduct problems. The subscales measuring internalizing problems are the anxiety, depression, and somatization subscales. The BASC-2 parent report form has high reliability ($\alpha > 0.90$) and moderate to high convergent validity.²⁰

Children's Depression Inventory. The Children's Depression Inventory, Second Edition (CDI-2)¹⁷ is a self-report measure that assesses cognitive, affective, and behavioral signs of depression in children and adolescents 7 to 17 years old. The CDI-2 measures symptoms of depression based on a total score and subscales. The CDI-2 has been found to be highly reliable in populations of pediatric patients ($\alpha = 0.88$ child report) and demonstrates sufficient concurrent and discriminant validity.²¹

Demographic Questionnaire. Parents completed a demographic questionnaire that gathered family information as well as a medical, psychological, and educational history of the affected parents and children.

Statistical Analysis

One sample *t*-tests were used to compare parent- and child-reported psychosocial functioning on the PedsQL to previously established samples of healthy patients and populations with other chronic illnesses. Scores of pediatric patients with FD on the CDI, BASC-2, and PedsQL were also compared with normative samples. Independent sample *t*-test comparisons between pediatric patients who were on ERT and those who were not on ERT were conducted to determine whether differences existed between groups on the PedsQL and the BASC-2. We also used independent sample *t*-tests across all measures to help explain any findings due to age or sex effects.

Results

The final sample consisted of 24 (10 males, 14 females) English-speaking pediatric patients with FD between the ages of 6 and 18 ($M = 11.96$, $SD = 3.2$), and 24 parents (9 males, 15 females), with each parent completing the survey for one affected child. Parent reports indicate that seven children (35.0%) (5 males, 2 females) were currently undergoing ERT, whereas 13 children (65.0%) (2 males, 11 females) were not. In general, the current sample is considered to be representative of the FD population (see ►Table 1 for full demographics).

Quality of Life

Comparisons of child and parent reports on the PedsQL 4.0 generic core scales indicate that children with FD differentially compare with healthy samples,¹⁸ oncology samples,²² and rheumatology samples.²³ The oncology sample included children diagnosed with a broad range of cancers, including acute lymphocytic leukemia, brain tumors, and lymphoma,²² whereas the rheumatology sample included children with juvenile rheumatoid arthritis, systemic lupus erythematosus, juvenile fibromyalgia, and other rheumatic diseases.²³ Patients with FD reported significantly lower QoL scores

Table 1 Demographic characteristics of pediatric patients with FD and their families

	Frequency	Percentage ^a
Sex (<i>n</i> = 24)		
Male	10	41.7
Female	14	58.3
Age (<i>n</i> = 24)		
6–8 y	4	16.7
9–11 y	5	20.8
12–15 y	13	54.2
16–18 y	2	8.4
Ethnicity of parents (<i>n</i> = 41) ^b		
Asian	4	9.8
Caucasian	33	80.5
Latino (Latin American, Hispanic)	3	7.3
Native American	1	2.4
Child current use of ERT (<i>n</i> = 20)		
No	13	65.0
Yes	7	35.0
Age in years when child started ERT (<i>n</i> = 8)		
5–8 y	4	50.0
9–11 y	2	10.0
12–15 y	2	10.0
Education of parents (<i>n</i> = 36) ^b		
High school diploma (or equivalent, e.g., GED)	7	17.5
Some college	14	35.0
Associate's degree	4	10.0
Bachelor's degree	9	22.5
Doctoral degree	2	5.0
Household income (<i>n</i> = 20)		
\$10,000–25,999	1	5.0
\$26,000–40,999	3	15.0
\$41,000–60,000	11	55.0
\$61,000–80,000	4	20.0
> \$200,000	1	5.0
Time away from school because of FD complications (<i>n</i> = 20)		
None	5	25.0
≤ 1 wk	3	15.0
1–2 wk	6	30.0
> 2 wk, < 1 mo	3	15.0
1–2 mo	2	10.0
2–3 mo	1	5.0
FD interferes with extracurricular activities, e.g., sports (<i>n</i> = 20)		
None	3	15.0
Little	5	25.0
Moderate	5	25.0

(Continued)

Table 1 (Continued)

	Frequency	Percentage ^a
Considerate	3	15.0
Extreme	4	20.0
Symptoms endorsed by parents of child with FD (parents selected as many as applied; <i>n</i> = 21)		
Fatigue	17	80.9
Gastrointestinal symptoms	15	71.4
Reduced ability to sweat	15	71.4
Temperature sensitivity	15	71.4
Exercise intolerance	11	52.4
Numbness/tingling	11	52.4
Episodic pain (e.g., acroparesthesia)	8	38.1
Dizziness	7	33.3
Headache	6	28.5
Cardiovascular problems	5	23.8
Sleep disturbance	5	23.8
Pulmonary problems	4	19.1
Corneal whirl/opacities	3	14.3
Tinnitus	3	14.3
Kidney problems	2	9.5
Dermatologic problems (i.e., angiokeratomas)	1	4.7
Increased sweating	1	4.7
Decision to start child on ERT (parents selected as many as applied; <i>n</i> = 8)		
Fear of worsening symptoms	8	100.0
Physical symptoms present	6	75.0
ERT was helpful for parent with FD	2	25.0
Physician recommended ERT	6	75.0
Family member or friend recommended ERT	1	1.25
Decision not to give ERT to child (<i>n</i> = 13)		
Lack of access due to ERT shortage	8	61.5
Reported worsening of symptoms due to shortage (<i>n</i> = 6)	4	66.7
Financial or insurance concern	3	23.1
Lack of physical symptoms	1	7.7
Other	1	7.7

Abbreviations: ERT, enzyme replacement therapy; FD, Fabry disease; GED, General Educational Development test.

^aPercentage refers to available *n*.

^bOne parent reported on their own and their partner's ethnicity, as well as their own and their partner's level of education. Discrepant *n* due to missing data.

when compared with healthy samples across nearly all health dimensions (total score: $p = 0.005$; physical health: $p = 0.003$; psychosocial health summary: $p = 0.010$; social functioning: $p = 0.026$; and school functioning: $p = 0.011$) (►Table 2). Similarly, parents of children with FD reported significantly lower QoL scores compared with healthy samples across all health dimension scores (total score, $p = 0.000$; physical health, $p = 0.000$; psychosocial health summary, $p = 0.001$; emotional functioning, $p = 0.008$;

social functioning, $p = 0.001$; and school functioning, $p = 0.004$).

►Table 3 displays a comparison between FD parent and child-reported QoL as compared with pediatric oncology and rheumatology reports. There were no statistically significant differences between these groups on any of the health dimension scores. However, in the comparison between pediatric patients with FD and those with rheumatic diseases several subscales of the PedsQL demonstrated differences

Table 2 Comparison between healthy and Fabry disease samples for the PedsQL 4.0 generic core scales child self-report and parent report

	Healthy sample ^a			Fabry disease sample				
Peds QL 4.0 core scales							Fabry vs. healthy	
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>t</i>	<i>p</i> Value
Child self-report								
Total score	401	83	14.79	21	71.58	16.41	−3.19	0.005
Physical health	400	84.41	17.26	21	70.39	18.97	−3.388	0.003
Psychosocial health	399	82.38	15.51	21	71.79	17.08	−2.84	0.01
Emotional functioning	400	80.86	19.64	21	74.76	21.48	−1.301	0.208
Social functioning	399	87.42	17.18	21	75	23.66	−2.405	0.026
School functioning	386	78.63	20.53	21	66.19	20.37	−2.799	0.011
Parent report								
Total score	717	87.61	12.33	20	66.47	22.03	−4.29	<0.001
Physical health	717	89.32	16.35	20	68.43	19.22	−4.86	<0.001
Psychosocial health	717	86.58	12.79	20	66.22	23.33	−3.904	0.001
Emotional functioning	718	82.64	17.54	20	66.75	24.19	−2.938	0.008
Social functioning	716	91.56	14.2	20	69.75	24.63	−3.961	0.001
School functioning	611	85.47	17.61	20	62.5	31.48	−3.264	0.004

Abbreviations: PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation.

Note: PedsQL scores range from 0 to 100, with higher scores indicating greater functioning and lower scores indicating poorer functioning. Bold values refer to statistically significant findings at the .05 level.

^aPedsQL 4.0 core scales healthy sample comparisons.¹⁸

that may indicate clinical significance when considering the less than 69.71 “at risk” cutoff score suggested by the PedsQL developers. Notably, these include psychosocial health ($M = 73.31$ vs. 66.22 , $p = 0.19$), social functioning ($M = 77.49$ vs. 69.75 , $p = 0.176$), and school functioning ($M = 73.40$ vs. 62.50 , $p = 0.138$).

Of note, an independent sample *t*-test indicated significant differences between younger FD patients and adolescents on both total child ($t[27] = 2.75$, $p = 0.007$) and parent reported QoL ($t[25] = 2.001$, $p = 0.035$), while higher QoL consistently being reported in younger children (Child Reported Total QoL: $M = 82.05$, $SD = 6.80$ vs. $M = 68.20$, $SD = 17.05$). Independent sample *t*-tests comparing QoL outcomes by sex found no significant differences between male and female children with FD.

Independent sample *t*-tests comparing QoL outcomes by sex found no significant differences between male and female children with FD.

Psychosocial Functioning

One sample *t*-tests were used to compare parent-reported BASC-2 scores to normed sample means ($M = 50$, $SD = 10$). The FD group was divided into a childhood group (ages 6–11, $n = 12$) and adolescent group (ages 12–18, $n = 14$). Parental report of adolescents with FD psychosocial functioning showed significantly higher scores on the BASC-2 internalizing problem subscales, including anxiety ($t = 3.21$, $p = 0.006$), depression ($t = 2.97$, $p = 0.01$), and somatization

($t = 5.079$, $p < 0.001$). Younger children with FD showed no significant differences in parent-reported internalizing behaviors from the normative group (→ **Table 4**), although the somatization subscale trended toward significance ($t = 2.097$, $p = 0.104$). Similarly, parents of younger children with FD did not report significant differences on behavioral symptoms index subscales or adaptive skills subscales (→ **Table 4**). However, parent reports of adolescents with FD indicate significant differences from normative samples on the attention problems subscales ($t = 2.308$, $p = 0.037$) and the adaptability subscale ($t = -2.70$, $p = 0.017$). Trends toward significance were also seen on the withdrawal subscale ($t = 1.995$, $p = 0.066$).

Independent sample *t*-tests were used to determine whether psychosocial functioning was related to the sex of the child with FD. Several scales approached significance (conduct problems: $t = -1.902$, $p = 0.071$, externalizing problems: $t = -1.33$, $p = 0.166$, attention problems: $t = -1.68$, $p = 0.106$; functional communication: $t = 1.62$, $p = 0.118$) with males consistently exhibiting poorer functioning.

Psychosocial Functioning, Quality of Life, and Enzyme Replacement Therapy Status

Independent sample *t*-tests compared parent-reported BASC-2 scores and PedsQL for children with FD currently receiving ERT (ERT+) and those not taking ERT (ERT−). The ERT+ group reported significantly lower scores on the attention

Table 3 Comparison between oncology, rheumatology, and Fabry disease samples for the PedsQL 4.0 generic core scales child self-report and parent report

Peds QL 4.0 core scales	Oncology sample ^a			Rheumatology sample ^b			Fabry disease sample						
	n	Mean	SD	n	Mean	SD	n	Mean	SD	Fabry vs. oncology		Fabry vs. rheuma- tology	
										t	p Value	t	p Value
Child self-report													
Total score	219	72.20	16.38	231	72.09	16.92	21	71.58	16.41	-0.17	0.863	-0.144	0.887
Physical health	219	71.79	21.80	231	68.12	22.52	21	70.39	18.97	-0.34	0.738	0.548	0.590
Psychosocial health	219	72.62	16.41	231	74.23	16.46	21	71.79	17.08	-0.22	0.827	-0.653	0.521
Emotional functioning	219	71.83	21.44	231	70.88	22.08	21	74.76	21.48	-0.63	0.539	0.828	0.417
Social functioning	219	76.84	20.31	231	80.75	18.27	21	75.00	23.66	-0.36	0.725	-1.113	0.279
School functioning	191	68.51	19.72	227	71.39	18.86	21	66.19	20.37	-0.52	0.607	-1.170	0.256
Parent report													
Total score	336	69.70	19.17	244	70.97	18.49	20	66.47	22.03	-0.66	0.520	-0.913	0.373
Physical health	336	68.75	24.98	244	66.72	24.12	20	68.43	19.22	-0.07	0.942	0.398	0.695
Psychosocial health	336	70.31	17.96	244	73.31	17.62	20	66.22	23.33	-0.79	0.442	-1.360	0.190
Emotional functioning	336	67.53	20.32	242	69.00	21.39	20	66.75	24.19	-0.14	0.887	-0.416	0.682
Social functioning	336	75.64	20.61	242	77.49	20.06	20	69.75	24.63	-1.07	0.298	-1.406	0.176
School functioning	250	66.40	23.19	229	73.40	21.07	20	62.50	31.48	-0.55	0.586	-1.549	0.138

Abbreviations: PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation.
Note: PedsQL scores range from 0 to 100, with higher scores indicating greater functioning and lower scores indicating poorer functioning.
^aPedsQL 4.0 core scales oncology sample comparisons.²²
^bPedsQL 4.0 core scales rheumatology sample comparisons.²³

Table 4 Comparison between normative and Fabry disease samples for the BASC-2 parent report by age group

BASC-2 scales	Ages 6–11 (<i>n</i> = 5)				Ages 12–21 (<i>n</i> = 15)			
	Mean	SD	Fabry vs. normative		Mean	SD	Fabry vs. normative sample	
			<i>t</i>	<i>p</i> Value			<i>t</i>	<i>p</i> Value
Externalizing problems	48.2	5.4	−0.745	0.498	53.6	12.68	1.099	0.29
Hyperactivity	49.2	2.95	−6.06	0.577	49.87	16.83	−0.031	0.976
Aggression	45.6	6.47	−1.522	0.203	50.8	9.42	0.329	0.747
Conduct problems	50.6	8.71	0.154	0.885	55.8	17.17	1.308	0.212
Internalizing problems	54.2	12.59	0.745	0.497	65.6	12.57	4.807	<0.001
Anxiety	51.2	12.46	0.215	0.84	60.27	12.39	3.211	0.006
Depression	47.4	9.74	−0.597	0.583	59.47	12.34	2.971	0.01
Somatization	61.4	12.16	2.097	0.104	68.2	13.88	5.079	<0.001
Behavioral symptoms index	48.4	9.84	−0.364	0.735	56.2	10.82	2.22	0.043
Atypicality	50.6	11.46	0.117	0.912	53.87	13.89	1.078	0.299
Withdrawal	50	15.07	0	1	55.73	11.13	1.995	0.066
Attention problems	47.8	12.68	−0.388	0.718	55.4	9.06	2.308	0.037
Adaptive skills	52.6	11.08	0.525	0.628	46.2	9.24	−1.593	0.133
Adaptability	51	10.89	0.205	0.847	44.33	8.12	−2.702	0.017
Social skills	53.6	10.9	0.739	0.501	49	10	−0.387	0.704
Leadership	52.6	10.49	0.555	0.609	48	8.92	−0.868	0.4
Activities of daily living	51.8	6.38	0.631	0.562	45.13	11.58	−1.628	0.126
Functional communication	52	9.77	0.458	0.671	47.8	9.81	−0.869	0.4

Abbreviation: BASC-2, Behavior Assessment Scale for Children, second edition; SD, standard deviation.

Note: Normative mean = 50, SD = 10. Higher standard scores on the BASC-2 are indicative of risk for each domain of functioning, except for adaptive skills, where lower standard scores are indicative of risk for problem. Bold values refer to statistically significant findings at the .05 level.

problems subscale of the BASC-2 ($p = 0.016$) and higher mean scores on the adaptive skill functioning subscale ($p = 0.012$). Parents of children in the ERT+ group also reported lower mean depression subscale scores that approached significance ($p = 0.129$), which are likely to be clinically meaningful due to an approximate 10-point difference between the scores.

When comparing differences in QoL outcomes utilizing the PedsQL, the ERT+ group had higher total mean scores that approached significance ($p = 0.194$). A mean 10-point difference was found between the scores of the ERT+ and ERT− groups, indicating that a significant difference may exist when examined in a larger sample.

Notably, the ERT + /ERT− groups appear comparable dependent on parental reports suggesting that there was no significant difference in symptom severity between the ERT + /ERT− groups ($p = 0.353$). However, a chi-squared analysis indicated that there was a significant difference between the number of male and female patients within the ERT + /ERT− groups, with the ERT+ group consisting of significantly more males ($\chi^2 [2, N = 20] = 7.1, p = 0.029$). While limited by the current sample size, future research should explore whether ERT produces differential, sex-specific improvements in functioning in children with FD.

Child-Reported Depression

One sample *t*-tests were used to compare child-reported symptoms of depression in pediatric patients with FD to the healthy sample using the CDI-2. Reports of total depression level did not yield significant differences, regardless of age ($p = 0.285$). The results on the CDI-2 subscales also were not significant (emotional, interpersonal, functional problems, negative mood, negative self-esteem, and ineffectiveness). Despite this, 21% of patients reported levels of depressive symptomatology within the clinical range (T score > 65 on the CDI-2).

Discussion

The current study is among the first to investigate the psychosocial impact of FD on children. Results indicate that adolescents with FD are differentially impacted than younger children, with parents reporting poorer QoL and greater rates of anxiety and depression in comparison to healthy children. The current study also found that children on ERT were reported to have fewer symptoms of depression, inattention, and possible increases in QoL. As stated by Muller (2006), poor psychosocial adjustment is highly predictive of poorer QoL in adults with FD.²⁴ Therefore, additional insight

contributed by the current study into the developmental trajectory of psychosocial and adaptive functioning deficits in individuals with FD may allow for the development of necessary interventions to enhance the overall QoL of patients with FD.

About psychosocial functioning, parental reports on the BASC-2 yielded significant findings in terms of internalizing behaviors, including anxiety, depression, and somatization in adolescents aged 12 and older. However, findings indicating clinical levels of somatization in adolescents with FD accompanied by slight increases in somatization in younger children with FD may suggest that somatization increases in children with FD as they age due to increases in disorder-related physical symptoms over time.²⁵ In contrast, self-reported depressive symptoms by children and adolescents were not statistically significant. Notably, 21% of children with FD reported levels of depressive symptoms within the clinical range. These findings suggest that rates of depressive symptoms in children with FD may be greater than previously anticipated, in line with previous findings reported by Cole et al (2007) suggesting that as many as 46% of adults with FD experience mild-severe levels of depression.^{13,26}

Parental reports of externalizing behaviors, such as hyperactivity, aggression, and conduct problems did not yield any significant differences between pediatric patients with FD and the normative sample. These findings are consistent with prior literature on children with chronic illnesses, which suggest that children with chronic illnesses may have a greater rate of internalizing rather than externalizing problems.²⁷ However, parents did report that adolescents experienced a greater number of behavioral symptoms than younger children with FD or the normative sample, characterized primarily by difficulties with attention and withdrawal.

Overall adaptive functioning was assessed via the BASC-2, complemented with parental reports of school attendance and participation. Parents reported that 75% of children missed some school as a result of symptoms of FD (60% of children missed < 1 month and 15% missed 1–3 months). Furthermore, symptoms of FD also affected 85% of children's ability to participate in extracurricular activities such as sports and other physical activities, which coincides with previous reports of 83% by MacDermot et al (2001).¹⁵ Notably, only on the BASC-2 "adaptability" subscale did parents report that FD significantly affected adolescents' ability to adapt to transitions or changes in plans as compared with a normative sample. Our findings failed to identify issues with adaptive functioning identified in previous research on adults with FD, such as difficulties with daily living skills.²⁸ However, this may be influenced by developmental expectations, as children with FD likely have less severe physical symptoms and fewer responsibilities than their adult counterparts.

About QoL, children with FD were reported to be experiencing poorer overall QoL as compared with healthy samples. Parents reported that children were experiencing decreased QoL in all domains (physical, psychosocial, emotional, social, school), whereas children's reports failed to identify issues in emotional functioning. However, taken with

findings on the depression subscale of the BASC-2 suggesting that parents identified depressive symptoms in adolescents with FD not reported by the adolescents themselves, this inconsistency either may be due to a sample characteristic or may suggest that children with FD have poorer insight into their emotional functioning.

In comparison to other chronic illness populations, children with FD were statistically similar to individuals with pediatric cancer or rheumatologic disorders (► **Table 3**). However, our results suggest that children and adolescence with FD may have greater clinical impairment in some aspects of social, psychosocial, and school functioning than children with rheumatologic issues, which may be contributed to by the multisystemic impact of FD.⁸ Taken with results suggesting that adolescents with FD experience more significant decreases in QoL, the differentiation between these groups may become more pronounced in adolescence. Rates of depression and anxiety in this population may also be compounded by the familial nature of FD, with older children becoming more aware of the long-term consequences of FD through increased exposure to their parent's experiences, which may not occur in children with pediatric cancer or rheumatologic disorders. Furthermore, unlike the pediatric cancer group, which included children in various stages of remission, the chronic nature of FD may also contribute to the decline in some aspects of functioning observed in adolescence in the current study.

The current study also found that children who had received ERT demonstrated fewer symptoms related to inattention and stronger overall adaptive functioning than those who had not received ERT. Taken with previous findings regarding adaptive functioning in children with FD, these findings suggest that while children with FD may not differ significantly from healthy children on their ability to perform activities of daily living, there may be a link between the use of ERT and their ability to adapt and transition to changes. However, this distinction was not observed in relation to anxiety scores between the two groups. Thus, children with FD may still have symptoms of anxiety, despite the use of ERT. It is possible that children with FD may still demonstrate symptoms of anxiety as a result of undergoing ERT infusions every few weeks, although results of the current study not indicate that children undergoing ERT were more likely to miss school than those not receiving ERT. The need to undergo frequent infusions may result in missing more days at school, which likely contributes to the maintenance of symptoms of anxiety in spite of ERT use.

As noted in ► **Table 1**, the current study also found that a lack of access to ERT due to the Fabrazyme shortage during the time the study was conducted was the primary reason that children were not on ERT (61.5%).²⁹ Parental reports suggest that the lack of access to ERT was responsible for the worsening of symptoms for several children, which suggests that some of the issues reported with psychosocial functioning and QoL in the current study may be impacted by the stress of the medication shortage.

Finally, the difference in depression scores between the ERT+ and ERT– groups approached significance, suggesting

that children who receive ERT may experience fewer depressive symptoms than those who had not received ERT. Similarly, group differences in QoL approached significance but did not fully confirm previous findings suggesting that ERT produces long-term increases on QoL for adults with FD.³⁰

Limitations

The relatively small sample size limits the statistical power and interpretability of the study findings. However, as with any rare disease, small sample size is likely to be a limitation in future investigations. Second, although children in the current study were all diagnosed prior to the age of 18, their FD phenotype (classic vs. late-onset) and genotype were not collected, which may limit generalizability of the results. Third, although attempts were made to include a control group (e.g., unaffected siblings), too few siblings participated in the study to render this a suitable control, which limits the internal validity of the results. Next, comparisons were made to previously established data on healthy and chronic illness samples, which may mean that there were discrepancies between the current study's data collection methods and those of the established findings. Furthermore, the interpretability of the current study findings, specifically means/SDs of the study measures, is complicated by the fact that it is unclear how equivalent the study sample and normative samples were in terms of demographics across study measures.

In summary, this study's findings expand the available medical and genetic literature of FD to include the psychosocial effects of FD on children. This study also highlights the need for an interdisciplinary approach in the treatment of FD. This would enable health care professionals to more effectively treat children and families facing medical and genetic complications, as well as psychosocial complications.

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