



Behavioral, social and school functioning in children with Pompe disease

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ABSTRACT

Purpose: To improve our understanding of the behavioral, social, and emotional functioning of children and adolescents with Pompe disease.

Method: Parents/guardians of 21 children (age 5-18y) with infantile (IPD) or late-onset (LOPD) Pompe disease on long-term enzyme replacement therapy completed three standardized checklists regarding their child's behavior: the Child Behavior Checklist (CBCL), Conners 3 Parent (Conners-3), Behavior Rating Inventory of Executive Function-2 (BRIEF2), and a survey of their child's educational services.

Results: Descriptive statistics were used to summarize the findings for each behavior checklist. Age standard scores from each checklist were reported for the IPD ($n = 17$, 9 females, mean age = 9y, 4 mo; SD = 3y, 8mo) and LOPD ($n = 4$, 1 female; mean = 11y, 2mo; SD = 2y, 1mo) groups. The majority of children with Pompe exhibited age-appropriate behavior and emotional functioning on these standardized checklists. However, negative mood symptoms, learning problems, decreased participation in structured social activities, and attentional difficulties were more frequently reported in children with IPD in comparison to same-aged peers. Parents of children with LOPD reported fewer problematic behaviors but endorsed negative mood symptoms and difficulties with peer relations. Most children received accommodations in regular education classrooms at school.

Conclusions: These standardized behavior checklists are useful screening tools for the early identification and treatment of behavior, emotional, and social concerns in children with Pompe disease.

1. Introduction

Pompe disease (glycogen storage disease type II) is a genetic disorder. A defect in the *GAA* gene causes a deficiency of lysosomal enzyme acid alpha-glucosidase (GAA), which leads to glycogen accumulation within cardiac, skeletal and smooth muscles, and the nervous system. Pompe disease is broadly classified into two groups; infantile Pompe disease (IPD) at the severe end of the clinical spectrum and late-onset Pompe disease (LOPD) with less severe clinical outcomes [1]. Children with classic IPD present with cardiomyopathy, progressive muscular weakness, and death from respiratory failure in the first year of life if untreated [2]. Individuals with LOPD present from as early as the first year of life to as late as the sixth decade, and are distinguished from individuals with IPD by the absence of cardiomyopathy in the first year of life [3]. With the availability of enzyme replacement therapy (ERT; recombinant human GAA, or alglucosidase alfa; Sanofi-Genzyme

Corporation, Cambridge, MA) since 2006, survivors with IPD are now entering young adulthood [1]. There are increasing concerns about the long term effects of Pompe disease; including the central nervous system involvement and the resulting impact on developmental outcomes [4]. To date, studies examining the cognitive functioning, academic skills, speech and language skills and visual-motor abilities of children and adolescents with IPD have shown considerable variability in their skill levels [5–10]. However, data on the behavioral, social, and emotional profiles of children and adolescents with Pompe disease are very limited.

In our earlier study, the adaptive behavior of five children with IPD (median age 6 years, 7 months) was measured using the Vineland Adaptive Behavior Scales-II, Interview Form; 4/5 children earned below average Adaptive Behavior Composite summary scores, which measure the child's functioning in the communication, daily living skills, socialization, and motor skills domains [6]. Significant weaknesses in the

Abbreviations: IPD, infantile Pompe disease; LOPD, late-onset Pompe disease; ERT, enzyme replacement therapy; CBCL, Child Behavior Checklist; Conners-3, Conners 3rd Edition Parent; BRIEF2, Behavior Rating Inventory of Executive Function-Second Edition; GAA, acid alpha-glucosidase; SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder; IEP, Individualized Education Program

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children's motor skills impacted all domains. Notably, the overall adaptive behavior of each child was lower than their cognitive ability. In our longitudinal follow-up study of 11 children with IPD (median age 11 years, 1 month), two children were being treated for attention-deficit/hyperactivity disorder, two experienced high levels of anxiety, and one child had an autism spectrum diagnosis [10,11]. However, given the prevalence of these conditions in the general population, it was unclear if these diagnoses were related to Pompe disease [6,10,11]. In a subsequent study, parent reports on the Child Behavior Checklist suggested mild social problems, behavior, and mood issues in 2/3 children with IPD (ages 7 and 16 years) [8].

To improve our understanding of the psychosocial impact of Pompe disease, the current study aims to describe; 1) the behavioral, social, and emotional functioning of children and adolescents with Pompe disease based on standardized behavior checklists completed by parents/guardians, and 2) the educational and support services received by children with Pompe disease.

2. Materials and methods

2.1. Participants

All participants were enrolled in a long-term natural history study of Pompe disease at Duke University Medical Center (Pro00072329). Included here are the year one data for 21 children (ages 5–18 years) with a confirmed diagnosis of IPD ($n = 17$) or LOPD ($n = 4$) receiving long-term ERT. Twenty children lived in the United States and one child traveled to Duke from South Africa for a clinical and research visit. The data were collected as part of the children's annual assessments by the same clinical psychologist (GAS). One parent/guardian for each child (19 mothers, one father and one grandmother) completed the study measures. Medical records of participants were reviewed for mental health diagnoses made by qualified professionals.

Duke University Institutional Review Board approved the study protocol. Written informed consent was obtained from each adolescent (at age 18 years) or the child's parent/guardian prior to all assessments. Verbal assent was obtained from children 6–11 years of age and additional written assent was obtained from children 12 years of age and older.

2.1.1. Data statement

To provide de-identified data and explore potential age-related patterns, the authors assigned subject numbers to the participants, based on the increasing order of age. Additionally, the authors decided not to reveal the sex of the participants to further protect their identity. Any additional data would be shared by request from a qualified investigator; contingent on the study protocol.

2.2. Behavior checklists

Parents/guardians completed three standardized behavior checklists regarding their child's typical behavior at home: Child Behavior Checklist for Ages 6–18 (CBCL), Conners 3rd Edition Parent (Conners-3), and the Behavior Rating Inventory of Executive Function - Second Edition (BRIEF2) Parent form [12–14]. These well-validated measures are widely used in clinical and research settings to evaluate a child's behavior, mood and social functioning. Each checklist contains individual items that comprise specific behavior scales. For each behavior scale, T-scores (mean = 50, SD = 10) are obtained based on the parent's rating of each item. T-scores < 60 are in the normal range, in comparison to a normative sample of peers of the same age and sex. For this study, T-scores between 1 and 2 SDs ($T = 60$ – 69) were considered to be clinically relevant (or borderline) and T-scores 2 SDs and higher ($T \geq 70$) were considered to be clinically significant (or problematic). The only exception was for the CBCL Competence scales, where T-scores = 31–39 were considered clinically relevant (or borderline), $T \leq 30$ were

clinically significant (or problematic), and T-scores ≥ 40 were normal.

2.2.1. CBCL

The CBCL is designed to screen for behavior problems, mood and social competence in children (ages 6–18 years) within the past six months based on parent/guardian report [12]. It contains 113 items that comprise eight Syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior), three Competence scales (Activities, Social, and School), and a Total Competence score.

2.2.2. Conners-3

The Conners-3 Parent form is a structured assessment of attention-deficit/hyperactivity disorder (ADHD) behaviors and several comorbid disorders in children (ages 6–18 years) [13]. It contains 108 items; which comprise six Content scales (Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Functioning, Defiance/Aggression, and Peer Relations). These items also comprise four Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Symptom scales: ADHD Predominantly Inattentive Presentation, ADHD Predominantly Hyperactive-Impulsive Presentation, Conduct Disorder, and Oppositional Defiant Disorder.

2.2.3. BRIEF2

The BRIEF2 is designed to screen children (ages 5–18 years) for difficulties in executive function [14]. The BRIEF2 Parent form contains 63 items in nine non-overlapping clinical scales which yield three summary scores: Cognitive Regulation Index (composed of Initiate, Working Memory, Plan/Organize, Organization of Materials, and Task Monitoring scales); Behavioral Regulation Index (composed of Inhibit and Self-Monitor scales), and the Emotional Regulation Index (composed of Emotional Control and Shift scales).

2.3. Survey of educational services

Parents/guardians also completed a survey developed specifically for this study regarding their child's school program and support services during the past year. The survey included details about the child's primary classroom placement (general education or special education), eligibility for special education programs (Individualized Education Program/IEP or 504 Plan), classroom accommodations, use of assistive technology, use of other aids (hearing aids, glasses/contact lens, mobility devices) and therapy services (physical, occupational, and speech/language therapies) provided at school.

2.4. Statistical analysis

Descriptive statistics were used to summarize the distribution of T-scores obtained on each behavior checklist, which included medians (5th and 95th percentiles), counts, means, and standard deviations. Scale scores on each behavior checklist were analyzed separately for those children with IPD ($n = 17$) and those with LOPD ($n = 4$). A heat map was used to visualize potential patterns within both groups.

3. Results

3.1. Participants

Patient characteristics and a description of their educational programs and support services are summarized in Table 1.

3.2. Behavior checklists

Each child's T-scores for all of the behavior checklist scales are included in a heat map (Fig. 1) containing three grades – lightest shade

Table 1
Characteristics of children with IPD (1–17) and LOPD (18–21), including their educational programs and support services.

ID	Age at assessment (years, months)	Aids and equipment used *		Classroom placement, school calendar	IEP/504 Plan	Accommodations	Assistive technology	Services provided at school			Individual counseling/psychotherapy sessions, number/month	
		Hearing aids	Glasses/contact lenses					Mobility devices	Physical therapy	Occupational therapy		Speech/language therapy
1	5 y	N	N	General, t	Y	Y	N	N	N	N	N	N
2	5 y, 2 m	Y	N	General, t	Y	Y	N	Y, d	Y, d	Y, d	Y, 1	N
3	5 y, 7 m	N	Y	General, t	Y	Y	Y, tablet computer with specialized apps for grammar/word predictions	Y, c, d	Y, c, d	Y, c, d	Y, 1	N
4	5 y, 10 m	N	N	Special, t	Y	Y	N	Y, d	Y, d	Y, d	N	N
5	6 y	Y	Y	Special, t	Y	Y	Y, FM system, tablet computer with specialized apps for grammar/word predictions	Y, d	Y, d	Y, d	N	N
6	6 y, 1 m	N	N	General, t	Y	u	N	Y, d	N	N	N	N
7	7 y, 3 m	N	N	General, t	N	N/A	N	N	N	N	N	N
8	7 y, 9 m	Y	Y	General, t	Y	Y	N	Y, d	Y, c	Y, d	N	N
9	8 y	N	Y	General, t	Y	Y	Y, communication device called Accent800 and digital notepad called reMarkable	Y, d	Y, d	Y, d	N	N
10	9 y, 9 m	N	N	General, t	Y	Y	Y, computer/laptop, smartphones	Y, d	N	N	N	N
11	10, 10 m	N	N	General, t	Y	Y	N	Y, d	Y, d	Y, c	N	N
12 mr	11 y	N	Y	General, t	Y	Y	N	N	N	N	N	N
13 mr	12 y, 1 m	Y	Y	Special, t	Y	Y	Y, computer	Y, d	Y, d	Y, d	N	N
14	13 y, 4 m	N	Y	Special, t	Y	Y	Y, laptop	Y, c	N	Y, c	Y, 1	N
15	14 y, 4 m	Y	Y	General, y	Y	Y	N	Y, d	N	Y, d	Y, 1	N
16	15 y, 4 m	N	N	General, t, private	N	N/A	N	N	N	N	N	N
17	16 y, 4 m	N	Y	General, t	Y	u	N	N	N	N	N	N
IPD: Median age 8 years; mean = 9 y, 4 m; SD = 3 y, 8 m; 8 males, 9 females												
18	9 y, 4 m	N	N	General, t	Y	Y	N	Y, d	N	N	N	N
19 mr	9 y, 6 m	N	N	General, t, private	Y	Y	N	N	Y, d	N	N	N
20	13 y, 7 m	N	N	General, t, home-schooled	N	N/A	N	N	N	N	N	N
21	14 y, 6 m	N	N	General, t	Y	N	Y, laptop	N	N	N	Y, 2	N
LOPD: Median age 11 y, 7 m; mean = 11 y, 2 m; SD = 2 y, 1 m; 3 males, 1 female												

Y-Yes, N-No, M-Male, F-female, y-years, m-months, AFO-ankle-foot orthosis, W-walker, t-traditional school calendar, y-year-round school calendar, d-direct therapy, c-consultation from a therapist, u-unknown or no response by the parent/caregiver, N/A-not applicable since the child does not have IEP/504 Plan, mr=Medical records reviewed for mental health diagnoses made by qualified professionals showed that Patient 12 was diagnosed with an autism spectrum disorder (ASD), Patient 13 had a mood disorder diagnosis, and Patient 19 had untreated ADHD. *These were the responses made by parents in the Survey of Educational Services, and may not reflect the recommendations by their clinical providers.

Heat Map of T-scores for individual scales on the behavior checklists (CBCL, Conners 3, and BRIEF2) for children with IPD and LOPD																													
		Legend: Normal (lightest shade), CR=clinically relevant (moderately shaded), CS=clinically significant (darkest shade)																											
		Children with IPD																	Children with LOPD										
Behavior Scales	Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	median	n affected	(CR+CS)	%	18	19	20	21	median	n affected	(CR+CS)
	Age of the child (years, months)	5	5.2	5.7	5.10	6	6.1	7.3	7.9	8	9.9	10.10	11	12.1	13.4	13.9	15.3	17					9.4	9.6	13.7	14.6			
	Sex	F	M	F	M	F	F	F	F	F	M	F	M	M	F	M	M	M	median	n affected	(CR+CS)	%	M	M	M	F	median	n affected	(CR+CS)
1. CBCL (ages 6-18)	Activities					39	29	52	49	28	32	30	49	29		40	37	36	37	8	67	40	40	47	41	42	0		
	Social					40	38	52	33	40	51	26	53	39		55	56	65	46	4	33	45	55	43	35	45	1		
	School					27	38	46	38	27	40	32	27	43		33	54	55	38	7	58	40	48	54	50	48	0		
	Total Competence					32	28	52	39	25	38	23	46	29		43	48	54	39	7	58	38	49	46	36	42	2		
	Anxious/Depressed					51	50	54	51	51	53	52	66	63		54	50	50	52	2	16	50	76	57	70	63	2		
	Withdrawn/Depressed					64	60	56	64	50	58	50	68	70		53	57	53	58	5	42	50	70	70	81	68	3		
	Somatic Complaints					50	61	50	66	53	50	66	67	61		67	50	50	57	6	50	53	61	67	50	58	2		
	Social Problems					64	52	54	54	52	56	57	73	66		54	51	50	54	3	25	51	90	58	64	66	2		
	Thought Problems					51	66	50	51	58	50	58	78	69		50	51	50	51	3	25	54	77	59	64	64	2		
	Attention Problems					55	57	53	55	55	50	62	75	65		52	52	50	55	3	25	55	69	51	51	57	1		
	Rule-Breaking Behavior					51	51	52	70	50	50	52	70	70		57	51	50	52	3	25	50	78	50	50	57	1		
	Aggressive Behavior					64	48	55	62	53	57	74	77	74		61	52	45	40	6	46	61	87	51	45	61	2		
2. Conners 3 (ages 6-18)	Inattention					46	56	56	49	50	49	67	90	79		66	59	41	43	4	31	40	90	45	48	56	1		
	Hyperactivity/Impulsivity					79	40	55	52	64	52	64	81	78		65	65	47	41	64	7	54	45	73	47	45	53	1	
	Learning Problems					50	41	57	40	52	58	70	65	56		42	49	51	38	5	15	69	63	39	46	54	2		
	Executive Functioning					47	51	57	90	41	47	56	77	70		48	66	43	43	4	31	43	90	41	51	56	1		
	Defiance/Aggression					65	43	54	49	49	49	64	74	64		58	52	48	54	5	38	49	90	90	90	80	3		
	Peer Relations					47	42	57	53	50	56	72	75		58	50	52	48	39	2	15	66	86	43	48	61	2		
	ADHD Predominantly Inattentive					47	54	55	51	50	47	66	90	75		65	63	41	43	5	38	42	90	45	46	56	1		
	ADHD Predominantly Hyperactive-Impulsive					45	55	57	67	43	50	52	68	55		45	75	43	44	2	23	44	90	43	55	58	1		
Conduct Disorder Scale					49	49	53	79	39	53	59	87	85		47	61	44	41	4	31	41	90	40	49	55	1			
Oppositional Defiant Scale					84	72	50	58	49	43	52	55	41	48		48	66	43	40	4	25	43	79	39	47	52	1		
3. BRIEF2 (ages 5-18)	Inhibit					59	78	53	53	44	59	59	39	59		44	78			3	13	39	54	39	55	47	0		
	Self-Monitor					67	64	70	52	56	43	56	53	46		52	46	88		5	31	52	72	41	68	58	2		
	Shift					83	82	64	53	43	46	51	77	43		46	80			5	31	46	70	41	60	54	2		
	Emotional Control					61	55	63	42	48	39	61	39	43		55	71			4	25	59	59	47	53	55	0		
	Initiate					61	77	52	50	58	44	55	44	58		50	53	76		3	19	52	69	39	44	51	1		
	Working Memory					53	55	47	42	40	40	56	37	40		50	58	77		1	6	58	50	43	53	51	0		
	Plan/Organize					49	66	62	44	53	53	47	49	57		44	53	73		3	19	62	46	36	49	48	1		
	Task Monitor					58	57	45	45	42	37	57	37	42		47	49	63		1	6	70	54	45	53	56	1		
	Organization of Materials					78	76	51	57	47	49	56	49	48		48	46	86		4	25	41	72	38	50	50	1		
	Behavior Regulation Index					79	76	68	53	49	44	54	68	44		49	46	86		6	38	49	72	41	65	57	2		
	Emotion Regulation Index					58	63	53	44	48	42	56	40	48		49	54	75		2	13	60	56	41	50	52	1		
	Cognitive Regulation Index																												

Fig. 1. Lightest shade (T-scores < 60, normal), moderately shaded areas (T-scores = 60–69, clinically relevant) and darkest shade (T-scores ≥ 70, clinically significant). The only exception was for the CBCL Competence scales, where the lightest shade (T-scores ≥ 40, normal), moderately shaded areas (T-scores = 31–39, clinically relevant) and darkest shade (T-scores ≤ 30, clinically significant).

(normal T-scores), moderately shaded areas (clinically relevant T-scores) and darkest shade (clinically significant T-scores). The heat map also provides the medians, percentages, and total number of children obtaining clinically relevant/significant scores for each scale. The parents of Patients 1–4 were not administered the CBCL and the Conners-3, as their children were below the age range for these measures. The parents of Patients 13 and 14 did not complete the BRIEF2 and CBCL, respectively, and therefore, were excluded from our analyses. Fig. 2 depicts the number of children with IPD who obtained clinically relevant/significant scores on individual scales, across the three behavioral checklists.

3.2.1. CBCL

On the CBCL, the median T-scores for the entire IPD group were clinically relevant on only three scales— Activities (37), School (38), and Total (39) Competence scales. The remaining nine scale scores were within the normal range (Fig. 1). However, the number of individual children with IPD obtaining clinically relevant/significant scores on the following scales was noteworthy: Activities (8/12), School (7/12), Social (4/12), and Total (7/12) Competence scales, and the Withdrawn/Depressed (5/12), and Somatic Complaints (6/12) Syndrome scales. Three or fewer children with IPD obtained clinically relevant/significant T-scores on the remaining five Syndrome scales (Fig. 1).

Patients 12 and 13 had clinically relevant/significant scores on most of the CBCL Syndrome scales, perhaps related to their autism spectrum disorder (ASD) and mood disorder diagnoses, respectively. These diagnoses were made previously by a mental health professional.

On the CBCL, the median T-scores for the entire LOPD group on the

Activities (42), Social (45), School (48) and Total Competence scales (48) were within the normal range. However, the group's median T-scores on the Anxious/Depressed (63), Withdrawn/Depressed (68), Social Problems (66), and Thought Problems (64) Syndrome scales were clinically relevant. Individual children with LOPD obtained clinically relevant scores on the Social (1/4) and Total (2/4) Competence scales and clinically significant scores on the Withdrawn/Depressed (3/4) and the Anxious/Depressed (2/4) Syndrome scales of the CBCL Syndrome scales, perhaps related to his untreated ADHD.

3.2.2. Conners-3

On the Conners-3 scales, the median T-scores for the entire IPD group were in the normal range (51–57), with the exception of the Learning Problems scale (64), which was clinically relevant. Individual children with IPD obtained clinically relevant/significant T-scores on the following: Learning Problems (7/13), Inattention (6/13), Peer Relations (5/13), Hyperactivity/Impulsivity (4/13), Defiance/Aggression (4/13), and Executive Functioning (2/13) Content scales, and the ADHD Predominantly Hyperactive-Impulsive Presentation (5/13), Oppositional Defiant Disorder (4/13), and ADHD Predominantly Inattentive Presentation (2/13) DSM-5 Symptom scales. As illustrated by the heat map (Fig. 1), most of the clinically relevant/significant scores were concentrated in the adolescent group (Patients 11–15).

For the entire LOPD group, the median T-scores on the Peer Relations (80) and Inattention (61) Content scales, and the ADHD Predominantly Inattentive Presentation (61) Syndrome scale were clinically relevant/significant. Individual children with LOPD obtained

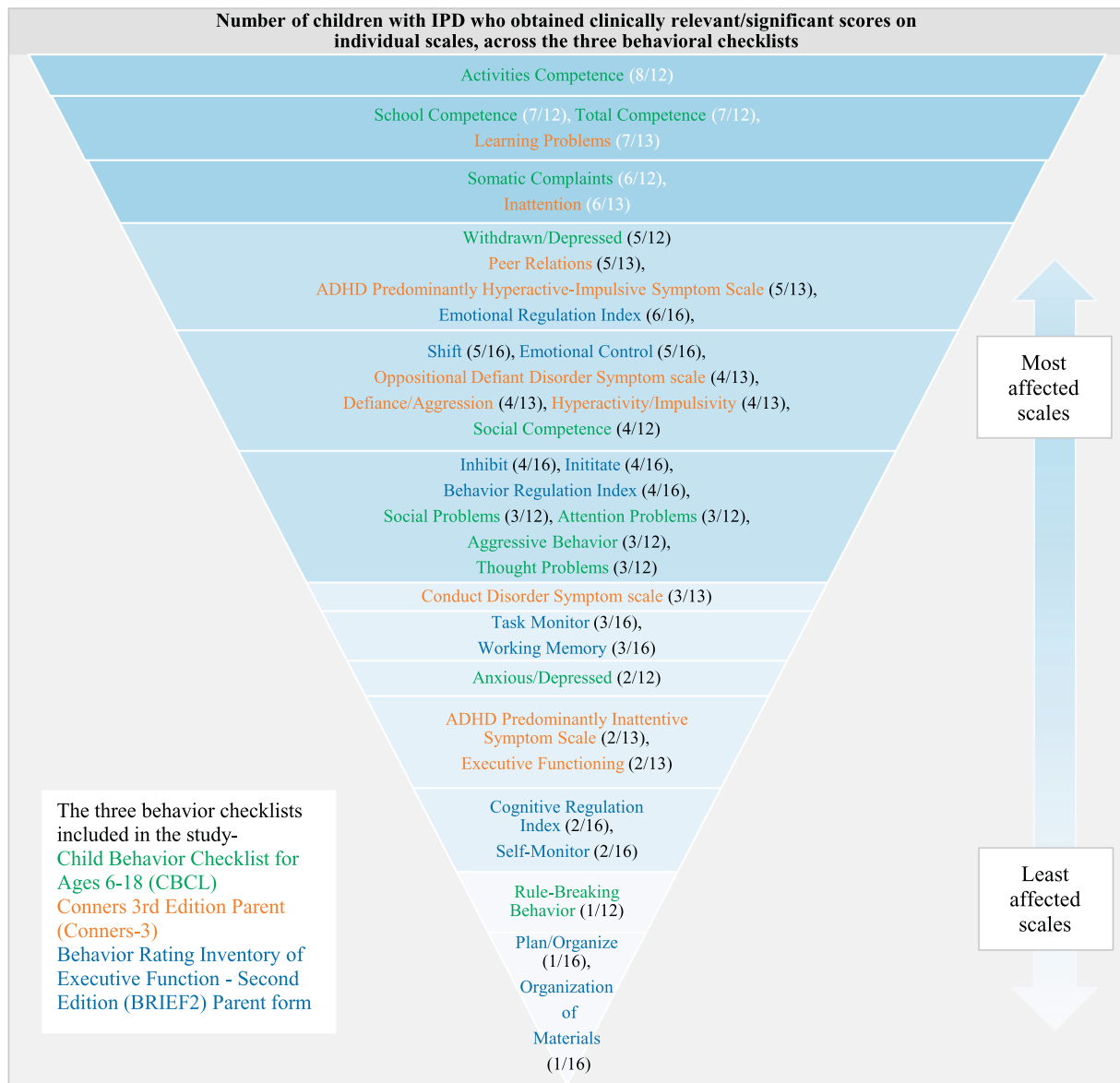


Fig. 2. Numerator indicates number of children with clinically relevant/significant scores on a scale, and the denominator indicates the total number of children with completed scale scores. All scales from one particular behavior checklist have a unique color (green is for CBCL, orange is for Conners-3, and dark blue is for BRIEF2).

clinically significant/relevant scores on the following: Peer Relations (3/4), Inattention (2/4), and Executive Functioning (2/4) Content scales, and the ADHD Predominantly Inattentive Presentation (2/4) Symptom scale. Of note, Patient 19 had 9/10 clinically significant and 1/10 clinically relevant scores on the Conners-3 scales. This could be due to the patient's concomitant ADHD diagnosis.

3.2.3. BRIEF2

On the BRIEF2 clinical scales and summary index scores, the median T-scores for the entire IPD group were in the normal range (46–54). However, individual children with IPD obtained clinically relevant/significant scores on the following: Shift (5/16), Emotional Control (5/16), Inhibit (4/16), Self-Monitor (2/16), Plan/Organize (1/16), and Organization of Materials (1/16) scales as well as the Emotional Regulation Index (6/16), the Behavior Regulation Index (4/16), and the Cognitive Regulation Index (2/16) summary scores. As illustrated by the heat map (Fig. 1), most of these clinically relevant/significant scores were found among the younger age group (< 6 years), Patients 1–3. Patient 12 with an autism spectrum disorder diagnosis, had clinically significant/relevant scores on all BRIEF2 scales and the

majority of the scales on the other checklists.

The median T-scores on all BRIEF2 scales for the entire LOPD group were in the normal range (47–58) in comparison to same-aged peers. However, the T-scores for the Shift and Emotional Control scales, and the Emotional Regulation Index were clinically relevant for Patient 21 and clinically significant for Patient 19.

3.3. Survey of educational services

The educational and support services received by each child with IPD and LOPD are reported in Table 1. Details about their specific accommodations and therapy services are listed in Table 2. Two children with IPD (Patients 7 and 16) and one child with LOPD (Patient 20) did not have an IEP or 504 Plan in place. Patient 7 was reportedly doing well at school, Patient 16 attended a private school which did not offer an IEP/504 Plan, and Patient 20 was home schooled.

4. Discussion

Children with chronic illnesses require continuous medical

Table 2
Accommodations and services provided to children with Pompe disease at school, through their IEP/504 Plan.

Total n=21	Children with an IEP/504 Plan and at least one accommodation	Accommodations (n)	Additional Support Services (n)
IPD n=17	n=15	Seating close to the teacher (7) Frequent breaks as needed or when tired (7) Customized seating (e.g., wheelchair, specialized chair) (6) Extra time to complete tests (6) Use of a computer or other devices in the classroom for written work (5) Extra time to complete assignments (5) Use of school elevators (5) Modified assignments (e.g., different work than peers) (4) Shortened assignments (2) Seating in the aisle (1)	Physical therapy (12) Speech/language therapy (10) Occupational therapy (8) Full-time one-to-one assistant provided at school (7) Time in a special education resource room (4) Nursing care/support (3) Instruction from an inclusion teacher (2) Part-time one-to-one assistant (1)
LOPD n=4	n=3	Frequent breaks as needed or when tired (2) Customized seating (e.g., wheelchair, specialized chair) (2) Extra time to complete tests/assignments (2) Use of computer or other device for written work (2) Use of school elevators (2) Eats on demand (no fixed lunch/snack break) (1)	Physical therapy (1) Occupational therapy (1) Time in a special education resource room (1)

n = number of children.

attention, lifestyle changes, and behavioral adaptation on a daily basis to cope with the challenges accompanying their illnesses [15]. These children often have additional stressors, including physical challenges, increased absenteeism at school, and academic difficulties [16]. They may also have a desire to be included in a peer group. Given the chronic nature of Pompe disease, management of children requires a multi-disciplinary team approach beginning early in life. The children's weekly or biweekly ERT infusions, visits to multiple specialists, and residual myopathy may pose significant challenges for their development. To our knowledge, this is the first study to explore the behavior, emotional, and social functioning in a large cohort of children with Pompe disease using standardized behavior checklists. Although children with Pompe disease experienced more difficulties in some behavior domains than same-aged peers, relative areas of strength were also apparent in these children and adolescents with Pompe disease (Figs. 1 and 2).

The standardized behavior checklists in the current study are well-validated, reliable, and widely used in research and clinical settings [12–14]. The availability of T-scores for each scale allowed for a comparison of individual participants with Pompe disease to the extensive normative samples of peers of the same age and gender. Only one previous study noted mild social problems, behavior, and mood issues in 2/3 children with IPD (ages 7 and 16 years) based on the CBCL, but did not report actual T-scores [8]. This study was a first step in systematically describing the behavior and emotional status of a sizable cohort of children and adolescents with Pompe disease. Additionally, the study details the support services received by the participants in a school setting.

Overall, the behavior and emotional functioning of the majority of children with IPD appeared to be age-appropriate, based on their CBCL Syndrome scale scores (Fig. 1). However, some parents of children with IPD reported difficulties on the Withdrawn/Depressed scale. They endorsed descriptors such as “Underactive, slow moving, or lacks energy” or “Too shy or timid,” as well as other items reflecting negative affect in their children, such as “Unhappy, sad, or depressed”. Additionally, several younger children in the study (< 6 years age) experienced problems in emotional regulation, as seen by their clinically relevant/significant scores on the BRIEF2's Emotional Control and Shift scales. These negative mood symptoms and emotional regulation difficulties may be related to the chronic nature of Pompe disease, and the associated medical issues that the children experience [2], as seen by their elevated scores on the CBCL Somatic Complaints scale. Children may require consultation from a mental health professional if these difficulties persist.

The current study also explored ADHD behaviors and other comorbid disorders in children with IPD using the Conners-3 checklist. Nearly half of these children obtained clinically relevant/significant scores on the Inattention scale. In addition, one third of the children with IPD obtained clinically relevant/significant scores on the ADHD Predominantly Hyperactive-Impulsive Presentation and Oppositional Defiant Disorder Symptom scales. However, these Symptom scale scores need to be interpreted cautiously. The items endorsed suggest that these children tend to be angry and resentful, argue with adults, and refuse to do what is asked, rather than being physically aggressive and hyperactive. Additionally, Patient 12 with an autism spectrum disorder and Patient 13 with a mood disorder had clinically relevant/significant scores on nearly all of the study scales.

In regard to their social functioning, the majority of children with IPD had clinically relevant/significant scores on the CBCL Activities Competence scale. These children participated less in sports and other activities (such as crafts) than same-aged peers as per the parents' reports. In addition, many of the children with IPD did not belong to any formal organizations, clubs, teams or groups with peers. This may be related to the limited time available for extracurricular activities given their medical needs (weekly or biweekly ERT infusions and follow-up with specialists), academic requirements, motor weakness, and fatigue [2]. Nevertheless, the children with IPD had close friends and got along well with peers and siblings, as reported on the CBCL Social Competence scale. Anecdotally, these children were adept at using social media outlets to connect with peers and socialize.

The current study also describes the functioning of children with Pompe disease within a school setting. Previous studies showed a range of cognitive and academic skills in children with IPD, including some children with a learning disability and/or problems with sustained attention and working memory [8,10,17]. In this cohort, more than half of the children with IPD obtained clinically relevant/significant scores on the Conners-3 Learning Problems scale. Their parents reported some difficulties in academic areas such as reading, spelling, and mathematics. Additionally, some adolescents with IPD experienced more difficulty concentrating and sustaining attention to tasks than would be expected for their age, possibly related to their time away from school. Completing ERT infusions at home or during the weekend can help reduce school absences. Children and adolescents with Pompe disease may also benefit from having assignments or tasks broken into smaller chunks, as well as access to a work area at home and school with minimal distractions [13]. Still, their ability to plan and organize tasks is a relative strength, as seen on the BRIEF2 measure of executive function.

Findings from the educational survey support our clinical impression that the majority of children with IPD attend and succeed at school. Most of the children in this study received one or more accommodations in their regular education classrooms. They qualified for special education services, as detailed in their IEP/504 Plan. This is reflected in the IPD group's clinically relevant/significant scores on the CBCL School Competence Scale. These accommodations and additional support services (such as occupational therapy) typically address the impact of the children's motor issues on their educational performance and stamina throughout the school day [2]. In general, the need for accommodations and school-based therapies is common for children with chronic medical conditions such as Pompe disease [18].

Overall, the parents of children with LOPD ($n = 4$) reported fewer problematic behaviors and emotions than those with IPD. Their scores on the CBCL Activities, Social, and School Competence scales were generally within the normal range in comparison to same-aged peers. However, clinically significant scores on the CBCL Withdrawn/Depressed (3/4) and Anxious/Depressed (2/4) scales suggested that children with LOPD may require screening and follow-up regarding their behavior and mood. Even though these children may be less impaired from a medical perspective, they could be at a risk for developing a mood disorder due to their chronic illness. Patient 19, with untreated ADHD at the time of the assessment, had clinically relevant/significant scores on most scales included on the three behavior checklists (Fig. 1).

Socially, it appeared that children with LOPD were similar to same-aged peers in their participation in sports and other activities, based on their scores on the CBCL Social and Activities Competence scales. However, 3/4 children with LOPD also obtained clinically significant scores on the Conners-3 Peer Relations scale, suggesting difficulties in this area and/or more limited opportunities to engage with their peers. Data from a larger cohort of children with LOPD is needed to better understand their social functioning.

The children with LOPD functioned well in regular education classrooms at school with fewer accommodations than the children with IPD. They were less likely to receive physical, occupational and/or speech/language therapies, as a part of their school program. As per the parent reports, their executive function skills seemed to be largely intact, however, their emotional regulation and ability to adapt to change require close monitoring.

The current study is limited by the small size of the sample, particularly the LOPD group ($n = 4$). However the inclusion of children with LOPD provides preliminary data, and enhances our understanding of the clinical spectrum of Pompe disease. Additionally, it provides insight regarding the behavior and cognitive difficulties reported in adults with LOPD [5,19,20]. This study is also limited by its inclusion of parent report data only. Future studies could incorporate teacher report and self-report questionnaires completed by the adolescents.

5. Conclusions

In conclusion, the study lays a foundation for the use of standardized behavior checklists to better characterize the behavioral, emotional, and social functioning of children and adolescents with Pompe disease over time. These measures are useful screening tools for clinicians to identify potential behavioral and emotional issues in children with Pompe disease in a timely manner, and to refer them for further evaluation and treatment [16]. The etiology of these issues is likely to be multifactorial given the chronic nature of the illness itself, potential medical complications, physical challenges faced on a daily basis, genetic influences, and/or social dynamics among others. Repeated administration of these checklists over time will also be helpful to identify when the children may be at high risk for specific difficulties or challenges. Longitudinal studies focusing on the behavior, emotions, and social challenges in children with Pompe disease will contribute to our understanding of the impact of Pompe disease across an individual's lifespan.

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Declaration of Competing Interest

Dr. Aditi Korlimarla, Dr. Gail A. Spiridigliozzi, Mihaela Stefanescu, and Stephanie L. Austin have stated that they had no interests which might be perceived as posing a conflict or bias.

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