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Cognitive and academic outcomes in long-term survivors of infantile-onset Pompe disease: A longitudinal follow-up

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Abstract

This study examines the long-term cognitive and academic outcomes of 11 individuals with infantile onset Pompe disease (IOPD) (median age = 11 years, 1 month, range = 5 years, 6 months through 17 years of age) treated with enzyme replacement therapy from an early age. All participants (7 males, 4 females) were administered individual intelligence tests (Wechsler or Leiter scales or both), a measure of their academic skill levels (Woodcock-Johnson Tests of Achievement), and a screening measure of visual-motor integration ability (Beery-Buktenica). Consistent with our earlier findings, median IQ scores for the entire group on the Wechsler (median = 84) and Leiter (median = 92) scales continue to fall at the lower end of the average range compared to same-aged peers. The median scores for the group on a measure of visual-motor integration (median = 76), visual perception (median = 74) and motor coordination (median = 60) were below average. Two distinct sub-groups emerged based on participants' average or below average performance on the majority of academic sub-tests. Those participants with below average academic skills ($n = 6$) demonstrated average nonverbal cognitive abilities on the Leiter, but had weaknesses in speech and language skills and greater medical involvement. Their profiles were more consistent with a learning disability diagnosis than an intellectual disability. Two of these participants showed a significant decline (15 and 23 points, respectively) on repeated Wechsler scales, but one continued to earn average scores on the Leiter scales where the verbal and motor demands are minimal. Participants with average academic skills ($n = 5$) demonstrated average cognitive abilities (verbal and nonverbal) on the Wechsler scales and less medical involvement. Their speech and language skills appeared to be more intact. However, both groups earned below average median scores on the Beery-Buktenica motor coordination task. This study highlights the importance of using appropriate tests to capture both verbal and nonverbal abilities, considering each individual's motor skills, speech and language abilities, hearing status and native language. This will allow for a more accurate assessment of whether there is a learning disability or an intellectual disability. Long-term outcomes may be related to the stability of an individual's

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expressive and/or receptive language abilities over time. Changes in the speech and language domain may account for the decline in IQ observed in some IOPD long-term survivors, reflecting a learning disability rather than a decline in overall cognition or an intellectual disability. These observations, in conjunction with neuroimaging, will further our understanding of the neurocognitive profile of long-term IOPD survivors.

Keywords

Infantile-onset Pompe; Cognitive; Academic; Visual-motor integration

1. Introduction

Pompe disease (glycogen storage disease type II) is a rare, progressive, autosomal recessive disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). In classic infantile-onset Pompe disease (IOPD), a complete or nearly complete lack of GAA enzyme activity causes severe symptoms, most notably affecting cardiorespiratory functioning and motor development. Untreated, the infantile form of the disease is fatal, with death occurring within the first 1–2 years of life. The availability of enzyme replacement therapy (ERT) with alglucosidase alfa in 2006 changed the course of the disease, allowing most children with the infantile form of Pompe the opportunity for improved survival [1]. Early clinical trials examining the treatment effects of ERT on infants with classic IOPD focused on long-term ventilator-free survival and cardiac response as the primary outcomes. With increased survival, a new disease course has emerged. Autopsy findings from infantile patients treated with ERT have revealed glycogen deposition in the central nervous system (CNS).

Given the potential for CNS involvement, IOPD research has shifted to consider the cognitive development of children with IOPD. The majority of published studies have focused on short-term outcomes, while few have described the children's cognitive development through adolescence. Data on academic outcomes are lacking.

In the pivotal study involving 18 infants with classic IOPD [2], measures of the infants' cognitive and motor functioning were obtained and later examined over their initial 12-month period of ERT (mean age of ERT initiation = 5 months, 2 days; range = 13 days to 7 months, 5 days) [3]. The majority of these infantile survivors ($n = 13$) demonstrated cognitive abilities at the lower end of the average range following 12 months of ERT, with no evidence of decline. There was also a strong correlation between measures of cognition (Bayley Scales of Infant Development, Second Edition: BSID-II) [4] and motor development (Alberta Infant Motor Scale: AIMS) [5]. Infants who showed a more limited motor response to ERT ($n = 4$) also had significant cognitive delays.

Similarly, Lai and colleagues [6] assessed the cognitive functioning of children with classic IOPD ($n = 13$) identified by newborn screening and treated very early with ERT (median age of ERT initiation = 10.5 days). at 6, 12, and 24 months of age. They demonstrated normal cognitive development on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [7], with no significant change in cognition over the 2-year study period.

As reported earlier by Spiridigliozzi et al. [3] cognitive development in these 13 infants was positively associated with motor development [6].

Yang and colleagues [8] also compared the cognitive outcomes of this same group of 13 newborns with classic, very early treated IOPD (median age of ERT initiation = 10.5 days) to 10 newborns with classic IOPD described by Chien et al. [9] who began treatment slightly later (median age of ERT initiation = 16 days). Both groups, identified through newborn screening, were selected for comparison because of their similar geographic location (Taiwan) and CRIM status (CRIM-positive). The children receiving very early ERT ($n = 13$) showed better cognitive (BSID-III) and motor (Peabody Development Motor Scale, Second Edition: PDMS-2) [10] developmental outcomes after one year compared to the cohort ($n = 10$) treated slightly later. These data suggest that newborn screening and early initiation of ERT are beneficial. Many of these children demonstrated cognitive skills within the average range as infants and toddlers [6,8].

To further our understanding of the long-term cognitive and adaptive functioning outcomes of children with classic IOPD, Spiridigliozzi et al. [11] examined seven children (median age = 7 years; range 4–8 years old), treated with ERT from an early age. Each child completed two to five standardized measures of cognition during the study period (i.e., BSID-II and/or BSID-III; Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) [12]; Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) [13]). The children with classic IOPD performed at the lower end of the average range on their most recent measure of general intellectual ability (median Full Scale IQ = 85; range = 73–109), compared to typically developing peers of the same age. Although there was substantial intra-subject variability noted across the study period, cognitive functioning did not decline over time. Two additional participants with atypical Pompe disease obtained above average Full Scale IQ scores and demonstrated gains in intellectual ability over time [11]. This study also highlighted the children's relative weakness on the Processing Speed subtests of the WISC-IV.

In the same study, Spiridigliozzi et al. [11] reported on the adaptive functioning of five children in the sample (4–8 years old) using the Vineland Adaptive Behavior Scales, Second Edition (Survey Interview Form) (VABS-II) [14] where adaptive behavior is defined as “the performance of daily activities required for personal and social sufficiency.” The overall Adaptive Behavior Composite (ABC) for this group (median ABC = 79, range = 72–105) was in the borderline range between average and significantly impaired, and lower than would be predicted given their Full Scale IQ scores. This was due, in large part, to weakness in the children's motor skills and its impact on everyday functioning, such as their ability to complete self-care tasks.

In another study of long term survivors, Ebbink and colleagues [15] examined the cognitive abilities of 10 children with classic IOPD treated with ERT over time. Those children born before 2004 ($n = 5$) were assessed serially using the BSID-II through 3.1 years of age and the Snijders Oomen Nonverbal Intelligence Test-Revised (SON-R) [16] at 5 years of age. Those children born after 2004 ($n = 5$) were assessed longitudinally using the Griffiths Mental Developmental Scales (Griffiths) [17,18] through 5 years of age. A total of 4

children (ages 6–12 years) later completed the WISC-III. One of the oldest children (approximately 11 ½ years old) obtained a WISC-III Full Scale IQ score in the lower end of the average range. The other three children earned WISC-III Full Scale IQ scores in the borderline range between average and significantly delayed. The researchers noted the importance of selecting appropriate measures to accurately assess the children's developmental and cognitive abilities, given the muscle involvement common among individuals with IOPD.

The same group [19] later described the cognitive decline observed in a 9-year-old patient with IOPD (CRIM-positive), who had been treated with ERT since 5 weeks of age. Reportedly, his cognitive abilities were in the normal to mildly delayed range up through age 6. At age 9, his cognitive abilities were in the moderate intellectual disability range. (WISC-III Full Scale IQ score = 48). This child also showed white matter abnormalities on a brain MRI.

In IOPD, abnormalities in brain imaging have been reported previously. These include delayed myelination, ventricular enlargement and subcortical white matter changes [9,19–22]. White matter abnormalities on MRI have been reported as early as 44 months [23]. However, the significance of these findings on the cognitive and academic abilities of individuals with IOPD is unknown.

Although researchers are examining the developmental trajectories of children with IOPD receiving ERT, the focus has been primarily on measures of cognitive abilities and not academic outcomes. The current study is a longitudinal extension of the Spiridigliozzi et al. report [11] and includes long-term follow-up cognitive assessments on the seven original patients (A-G) and four additional patients (J-M) with classic IOPD from 5 years, 6 months through 17 years of age.

This study is the first detailed report on the long-term developmental outcomes in adolescents with IOPD. This study is unique in that it includes standardized measures of academic functioning, specifically the children's acquisition of reading, math and written language skills. In addition, this study includes a measure of the children's visual-motor integration skills. Although the focus has historically been on the children's proximal weakness, we were interested in examining their distal weakness as well. The study also sheds light on the importance of test selection and interpretation when measuring the children's cognitive abilities, so that their strengths and needs are characterized appropriately and they receive optimal educational supports.

2. Methods

2.1. Participants and procedures

Participants for the present study were drawn from a long-term natural history study of children and adolescents with Pompe disease at Duke University Medical Center. The study was approved by the Duke Institutional Review board and written informed consent was obtained from each child's parents or legal guardian. Early data from seven of these participants (A-G) were reported by Spiridigliozzi et al. [11]. Participants J through M were

enrolled later and have not been included in any other publications. Children with atypical Pompe (presentation in the first year without cardiac involvement) were excluded from the current study. Children with IOPD who were CRIM-negative were also excluded, as they were not administered developmental assessments on a regular basis.

2.2. Measures

2.2.1. Clinician assessments—Multiple individualized assessments of cognitive functioning and academic skills were conducted using standardized tests and administration procedures. All tests were administered by the same clinical child psychologist (GAS) at Duke University Medical Center, who was very familiar with this population and had extensive experience in psychological assessment. The only exception was one evaluation (participant J at 11 years, 1 month) completed at a major medical center near the child's home. All testing sessions were completed in a non-medical, low-stimulation room while the child's parent(s) observed via a two-way mirror. Sessions were typically scheduled in the morning to minimize the possible impact of fatigue on test performance. The participants wore their eye glasses and hearing aids during the assessments.

2.2.1.1. Cognitive functioning—Cognitive functioning was assessed using the most appropriate standardized intelligence (IQ) test for each participant, based on the individual's age, the presence/absence of significant hearing and/or speech and language difficulties, and the participant's native language. The Wechsler scales were administered when deemed appropriate by the clinical child psychologist to capture multiple domains of the child's cognitive abilities. The WPPSI-III or Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WPPSI-IV) [12,24] was administered to children 3–5 years of age. The Wechsler Intelligence Scale for Children, Fourth or Fifth Edition (WISC-IV or WISC-V) [13,25] was administered to children 6–15 years of age and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [26] was administered to participants 16 years of age and older. Each of the Wechsler scales are designed to assess cognitive functioning across a number of domains, such as verbal comprehension, visual spatial, working memory, and processing speed. The clinician provides verbal instructions for all of the Wechsler subtests. The participant is required to speak their response for some subtests and point or use a pencil for others.

Children 3 years of age and older with significant hearing and/or speech and language difficulties or impairments or those with a native language other than English were administered the Visualization and Reasoning Battery of the Leiter International Performance Scale-Revised (Leiter-R) [27] or the Cognitive Subtests of the Leiter International Performance Scale-Third Edition (Leiter-3) [28] rather than the Wechsler tests. The Leiter-R and Leiter-3 are standardized nonverbal assessments designed to measure IQ independent of the individual's language and motor ability. The clinician presents item prompts on the Leiter using pantomime, gestures, and manipulatives and the participant indicates his/her responses by pointing or moving blocks rather than speaking.

For all cognitive measures, an overall composite (i.e., Full Scale IQ score on the Wechsler scales or Nonverbal IQ score on the Leiter scales) was computed as an estimate of general

intellectual ability. For the Wechsler scales, composite scores were also calculated to represent intellectual functioning in specific cognitive domains (e.g., Working Memory). All IQ and composite scores are standardized scores, with a mean of 100 and a standard deviation of 15. Scores between 85 and 115 are considered to be in the average or normal range in comparison to typically developing, same-aged peers. Scores between 70 and 84 are in the borderline range, between average intelligence and mild intellectual disability. Although the Wechsler and Leiter scales are designed to estimate overall cognitive functioning, scores from these two measures are not interchangeable as the Wechsler scales require the use of expressive and receptive language skills and the Leiter scales minimize language skills.

2.2.1.2. Academic skills: The Woodcock-Johnson III and Woodcock-Johnson IV (WJ-III and WJ-IV) Tests of Achievement (Form A) [29,30] were administered to children ages 6 and older as a measure of their academic skill levels. The WJ-III and WJ-IV measure participants' academic skills in three specific domains (reading, written language, and mathematics). Age standard scores are reported for each subtest and cluster (i.e., Broad Reading, Broad Written Language, Broad Mathematics, and Academic Fluency). The Academic Fluency cluster consists of three timed subtests. Once again, scores between 85 and 115 are considered to be in the average or normal range in comparison to typically developing, same-aged peers.

2.2.1.3. Visual-motor integration: The Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition and 6th Edition (VMI) [31,32] were administered to the participants at ages 4 and older to examine their coordination of visual and motor functioning (i.e., visualmotor integration ability). The VMI consists of one untimed subtest (Visual-Motor Integration) and two supplemental timed subtests (Visual Perception and Motor Coordination). Standard scores between 85 and 115 are in the average range in comparison to other individuals of the same age. All study participants completed at least one administration of the VMI.

2.2.1.4. Parent-report: During the clinical interview portion of each assessment visit, parents were asked by the examiner to describe any educational and support services their child was currently receiving. Data from these interviews regarding each child's school placement, special education services, and participation in therapies (such as physical therapy, speech and language therapy, and occupational therapy) are presented in Table 2.

2.3. Data analysis—Data were compiled and examined via tables in MS Word. Descriptive statistics were performed using SPSS Statistic, version 24.

3. Results

3.1. Study participants

Eleven children (7 males, 4 females) with IOPD (median age = 11 years, 1 month; range = 5 years, 6 months to 17 years, 0 months at the time of latest assessment) who began receiving ERT prior to six months of age² (with the exception of Subject K who started ERT at 25 months) were enrolled. All of the study participants were CRIM-positive and were

diagnosed with cardiomyopathy within the first year of life. The majority of participants live outside of the Southeast region of the United States (including abroad) and travel to Duke University Medical Center for clinical evaluations. All have been followed longterm at Duke.

Participants were divided into two groups based on their academic skills. One group of participants were those that performed below average on most measures of academic functioning (below average group, $n = 6$) while the second group performed in the average range on their latest assessment of academic functioning (average group, $n = 5$).

Descriptive information regarding each participant's motor status at the time of their latest psychological evaluation is included in Table 1. None of the participants required invasive or non-invasive ventilation. Six of the participants were able to ambulate independently, with or without ankle-foot orthotics (AFOs). Three participants (B, D, E) used wheelchair support full-time and the others used wheelchair support for longer distances. With one exception (A), all participants had some degree of dysarthria as reported by a speech pathologist with experience in Pompe disease. Nine participants had hearing loss and 7 required use of hearing aids at the time of their most recent psychological evaluation.

The participants' academic settings and support services at the time of their latest psychological evaluation are summarized in Table 2. Six participants were based in an age-appropriate general education classroom setting. Three children had the support of a full-time paraprofessional while in school. One child received homebound instruction exclusively at the request of his guardian, while 3 others were receiving homebound instruction or tutoring in addition to attending school. Seven participants were receiving speech-language therapy through the public school system or privately. Five children were receiving direct or consultative services from an occupational therapist. Seven children were receiving physical therapy services in school and/or privately.

3.2. Cognitive functioning

3.2.1. Entire group—Table 4 includes the results from each participant's most recent IQ and academic achievement test administration and summary statistics for the entire group. Available Full Scale IQ scores from the Wechsler scales ($n = 8$) ranged from 51 (significantly below average) to 116 (above average) (median = 84.0) in comparison to same-aged peers. Nonverbal IQ scores from the Leiter scales ($n = 6$) ranged from 69 (significantly below average) to 99 which is average in comparison to same-aged peers (median = 92.0). For the 3 participants who completed both the WISC and the Leiter at the same time point, Nonverbal IQs from the Leiter scales tended to be higher or essentially the same as Wechsler Full Scale IQ scores.

3.2.2. Below average performing group and average performing group academically—Table 5 includes the IQ and academic achievement summary statistics for these two subgroups of participants. For those participants ($n = 6$) in the below average performing group, the median Wechsler Full Scale IQ score was 60.0 (range = 51–68) while

²Participants over the age of 9 years received ERT prior to FDA approval through participation in early clinical trials of Myozyme¹.

the median Leiter Nonverbal IQ was 96.0 (range = 68–99). The 36 point difference between these median test scores is >2 standard deviations. Median scores for Broad Reading (51.0), Broad Written Language (53.0), Broad Mathematics (58.5) and Academic Fluency (55.0) were all significantly below average for this group.

For those participants in the average performing group ($n = 5$), the median Wechsler Full Scale IQ score was 105 (range = 80–116). Only one child in this group was administered the Leiter-3 and earned a score of Nonverbal IQ score of 75, which was very similar to his Full Scale IQ of 80. Median scores for Broad Reading (101.5), Broad Written Language (106.3), Broad Mathematics (102.5) and Academic Fluency (102.5) were all in the average range for this group.

3.3. Cognitive assessments over time

Table 3 shows the latest IQ assessments reported in 2012 [11] for the 7 participants (A-G) included in this study and subsequent IQ assessments. The repeated IQ assessments for the 4 participants (J-N) added after the Spiridigliozzi et al. 2012 report are also included in Table 3. Since the appropriate version of the Wechsler and Leiter scales administered changed over time, depending upon the age of the child and updates to the tests themselves, an increase or decrease in IQ scores cannot be absolutely determined, although they would be expected to remain in the same range.

For those seven subjects who had repeated Wechsler scales, four (A, B, G, M) essentially obtained the same Full Scale IQ, one (F) showed an increase (20 points), and two (C, J) declined (23 and 33 points, respectively) from the 2012 report to present. For those five children who had repeated Leiter scales, one (B) essentially earned the same Nonverbal IQ, three showed an increase (C, D, E; 11, 12 and 16 points respectively) and one (L) showed a decline (8 points) from their first to most recent Leiter administration.

Table 3 also illustrates the considerable fluctuation within individual subjects' scores from the Spiridigliozzi et al. 2012 report to the present. The cognitive trajectories over time also varied between subjects.

3.4. Wechsler composite scores

Table 6 shows the Full Scale IQ and composite scores for the Wechsler scales administered most recently. Nonverbal IQ scores for the Leiter scales are also included for ease in comparison. For 2/8 participants (F, G) who completed a Wechsler IQ test, their score on the Processing Speed composite was their lowest composite score. For 1/8 participants (A) who completed a Wechsler IQ test, their score on the Processing Speed composite was their highest composite score. Processing speed is not measured on the Leiter scales, as all of the cognitive subtests are untimed.

3.5. Visual-motor integration

Table 7 includes participants' age standard scores on the three subtests comprising the VMI-5th and VMI-6th. The median score on the VMI subtest was 76, the median score on the Visual Perception subtest was 74, and the median score on the Fine Motor subtest was

60. These findings highlight the fine motor weaknesses of the participants, particularly when there are time limits imposed.

4. Discussion

As individuals with IOPD live longer, its impact on the CNS and cognitive function remains an unanswered question. Findings like sensori-neural hearing loss and abnormalities on brain MRIs point toward the involvement of the CNS in long-term survivors. There are previous reports of young IOPD survivors with cognitive functioning at the lower end of the average range, including a single case report of cognitive decline. This study is the first to report on both the cognitive and academic skills of the oldest surviving children and adolescents up to age 17 years with IOPD using a battery of standardized test measures. This study also provides detailed longitudinal cognitive data on children and adolescents with IOPD.

When considering the entire group of 11 study participants (median age = 11.1 years), median IQ scores on the Wechsler and Leiter scales continued to fall at the lower end of the average range in comparison to same-aged peers, although IQ scores on the Leiter tended to be higher. This was consistent with our earlier report [11] on seven of these children, when the median age of the group was 7 years.

However, when taking a closer look at the data for individual participants, we recognized that there were two distinct subgroups – an average performing group ($n = 5$) and a below-average performing group ($n = 6$) on the majority of cognitive or academic subtests (Table 5). Although there were no significant differences at the start of ERT for these two groups in regard to their age, CRIM status, and ventilator status, features in common for the below-average performing group included bilingualism ($n = 3$) and more comorbidities, both related and unrelated to IOPD ($n = 4$), as seen in Table 1.

Participants in the below-average performing group also required greater educational support services. Four children received their academic instruction in special education classrooms and one required a full-time assistant to remain in a general education classroom. One child receives home-bound instruction and tutoring exclusively. Three of these children are also receiving treatment for their co-morbid conditions, including attention-deficit/hyperactivity disorder, anxiety, emotional lability and an autism spectrum disorder. However, it is not known at this time if these conditions are related to Pompe, as they are common in the general population. All of these children have some degree of hearing loss, which likely contributed to the group's lowest academic summary score in reading (median WJ Broad Reading composite = 51, $n = 4$). Scores on the WJ Passage Comprehension subtest were particularly low (median = 39), suggesting a significant weakness in their reading comprehension ability. Three of the four children who completed the WJ-IV Writing Samples subtest also showed a significant weakness in their ability to organize and write sentences, in comparison to the average performing group.

Due to their speech articulation difficulties, motor weaknesses and bilingualism, 5 of the 6 individuals in the below-average performing group were administered the Leiter-3 as a

measure of their cognitive ability. The majority ($n = 4$) earned Nonverbal IQ scores in the average range. All 5 of these participants completing the Leiter-3 showed a significant difference (> 15 points) between their Nonverbal IQ and their WJ Composite scores (i.e., Broad Reading, Broad Mathematics and Broad Written Language). This discrepancy between the subjects' IQ and academic achievement suggests that an underlying learning disability may be present, rather than a cognitive decline or an intellectual disability. More specifically, these participants may be exhibiting a learning disability that is impacting most heavily on academic tasks with a language component, such as reading comprehension and written language.

The below-average performing group also illustrates the point that the IQ tests administered to individuals with IOPD must be carefully selected and interpreted. Given our experience with this population and their varying degrees of motor involvement, we carefully selected our test battery to help capture their true cognitive abilities. We also considered each participant's speech impairments, and whether or not they were native English-language speakers. It appears that the language and motor demands of the Wechsler tests may underestimate the actual cognitive abilities of children and adolescents with IOPD, especially in the below-average group. For these children, the Leiter-3 was the most appropriate test due to their speech difficulties and/or the fact that English was their second language. Using the Leiter-3 and the WJ, a discrepancy was noted between the participant's Nonverbal IQs and their academic skills. This profile is consistent with a learning disability diagnosis, which could have been missed if a nonverbal IQ test had not been performed. An intellectual disability diagnosis would not be appropriate for individuals in this group who earned an average Nonverbal IQ score even though they earned significantly lower Full Scale IQ scores on the Wechsler scales.

It is critical that psychologists assessing the cognitive abilities of individuals with IOPD select tests that are in line with the child's relative strengths so that his/her cognitive abilities will be accurately measured and they are not incorrectly labelled. A diagnosis of a learning disability versus an intellectual disability can have a direct bearing on a child's classroom placement, the type of educational support services received, and expectations for their academic gains. These diagnoses also may influence how a parent, teacher or therapist views and interacts with the child.

Of note, within the average performing group, two of the five participants are now in high school. These adolescents were also the oldest participants in the study. Their scores on IQ testing and academic skills (in comparison to same-aged peers) were the highest of the entire sample. Some of their academic subtest scores on the WJ-IV were above average in comparison to other students their age. Three of the participants in this group have no hearing loss and none were bilingual. Two have a comorbid diagnosis. All of these participants attended general education classes, and two had a full-time paraprofessional providing support for their physical needs at school. Overall, the participants comprising the average performing group were less involved medically than those in the below-average group, requiring no or less use of a wheel-chair and hearing aids (Table 1).

All participants in the average performing group ($n = 5$) were administered a Wechsler scale as the most appropriate measure of their cognitive ability. All of these participants had academic skills at the expected levels for their age and did not show a significant difference between their Wechsler Full Scale IQ score and the WJ Composite scores. None of their profiles of skills suggested a learning disability diagnosis. Participant B actually scored higher on the achievement testing than might be expected, given his below average Full Scale IQ. In contrast to the low-performing group, the median score on the WJ Writing Samples subtest (109.5) for the average performing group was their highest subtest score. All four participants completing this untimed task scored at the upper end of the average range. Their ability to formulate and write sentences in response to a prompt was a particular area of strength. Scores on the WJ Passage Comprehension subtest were more variable, but still significantly higher than those obtained by the below-average group. The average performing group demonstrated stronger language comprehension and written language skills than the below-average group.

It is also interesting to note that the median score on the WJ Math (Facts) Fluency subtest (101) was the highest subtest score for the entire group of participants (Table 4). This task involves solving simple arithmetic problems quickly. As such, it relies more on a child's nonverbal, visual spatial skills than language abilities.

Although two subgroups of participants have become apparent over time, determining the developmental trajectory for each individual was more challenging. This was due to the fact that different versions of the Wechsler scales must be administered at different ages and the fact that the tests themselves have been revised over time.

In the present study, the cognitive decline described by Ebbink et al. [19] (27 points on the WISC-III from age 6 to 9 years in one child) was seen in two children using the Wechsler scales. We defined a significant decline as a 15 or more point decrease in a child's Full Scale IQ. Participant C's initial decline (15 points) was seen from 6 years, 7 months to his testing completed at 8 years, 11 months of age. Participant J's decline (23 points) was seen from 8 years, 3 months to the testing completed at 11 years, 1 month. For those children who had completed a Leiter scale two or more times, a less dramatic decline (10 points) was seen for one child. Participant L's decline was seen from age 6 years, 1 month to 7 years, 9 months of age. All of these participants were included in the below-average performing group based on their most recent testing.

However, our data indicate that a decline in Full Scale IQs on the Wechsler scales must be interpreted with extreme caution in children with IOPD. While participant C earned a Full Scale IQ of 60 on the WISC-V at 12 years, 1 month of age, he earned a Nonverbal IQ of 99 on the Leiter-3 at the same age (Table 3). This Nonverbal IQ in the average range is not consistent with an intellectual disability diagnosis. Rather, it suggests the possibility that the child's expressive and/or receptive language abilities (emphasized on the Wechsler scales) may be changing over time relative to peers, rather than his overall cognition. Alternatively, it is possible that an individual's language ability may be more heavily impacted by their IOPD than other cognitive abilities. When considering all of participant C's most recent

cognitive and academic skill levels, a language-based learning disability is the most appropriate diagnosis.

Spiridigliozzi et al. [11] described a relative weakness on the Processing Speed composite of the WISC-IV for some participants. This observation underscored the importance of looking beyond an overall measure of cognitive ability to determine participants' relative strengths and weaknesses. This was subsequently reported by Ebbink et al. [15,21]. In examining the latest administrations of a Wechsler scale for 8 participants in this study (Table 6), the Processing Speed Index was the lowest score for only two individuals. These were the high school students and oldest participants in the sample. Both individuals displayed high average or significantly above average verbal comprehension and expression skills on the Wechsler scales, indicative of strong language ability. In contrast, their scores on the Processing Speed composite fell at the lower end of the average range. The one participant where the Processing Speed composite was their highest composite score demonstrated much weaker verbal comprehension and expression skills. However, this child scored in the average range on the nonverbal Leiter-3. As the Leiter Cognitive Subtests are untimed and do not measure visual processing speed, this skill was not assessed for the participants in our below-average group. It is possible that a visual processing speed weakness was present in these below-average group participants, but not captured in their assessments using the Leiter. Future studies could incorporate the Wechsler Processing Speed subtests as part of the test battery for all participants, including those who are administered the Leiter-3 as the most appropriate measure of their cognition.

Due to our observations of distal weakness in children with IOPD, we also included the Beery-Buktenica VMI in the test battery as a measure of their eye-hand coordination. This screening measure includes a timed Motor Coordination subtest which requires the child to use a pencil to trace designs while staying within the boundaries. As seen in Table 7, the median score for the Motor Coordination subtest is particularly low for our participants and is significantly below average in comparison to same-aged peers. Furthermore, the median scores for the latest administration of all Beery-Buktenica subtests are significantly lower than would be expected given the median Full Scale IQ and Nonverbal IQ scores for the entire group. Functionally, this finding confirms our observation of the children's distal weakness, in addition to their proximal weakness. As a result, children with IOPD are likely to have a great deal of difficulty keeping pace with the handwriting demands at school, particularly when there are time limits imposed. This weakness can also impact their performance on classroom and standardized testing, such as IQ tests. Only four of the participants in our group receive direct occupational services at school targeting their fine motor skills and none receive private occupational therapy. We propose that an occupational therapist with expertise in assistive technology should be included as part of each child's multidisciplinary treatment team, particularly when they enter school. This professional can help address a child's need for an alternative to handwriting, such as using a tablet or computer to complete written assignments. Other accommodations include providing the child with extra time to complete written work or shortening the length of assignments. Given the appropriate support services and accommodations, children with IOPD will be better able to demonstrate their true capabilities.

Several reports describe brain development over time in individuals with IOPD using imaging data, such as ultrasound, MRI, computerized tomography (CT) scans, and magnetic resonance spectroscopy (MRS) [19,21,33], particularly in terms of white matter abnormalities, extra axial fluid collection and myelination defects. Chien et al. [33] described delayed myelination and ventricular dilation in five infants with IOPD upon the initiation of ERT. Austin et al. [22] found ventricular enlargement and/or extra-axial cerebrospinal fluid accumulation in 14 of 23 children with IOPD, as well as delayed myelination in two of those children. Their findings also included deep white matter changes in two of three CRIM-positive children imaged after 10 years of age, with one demonstrating a basilar artery aneurysm. Importantly, both of these studies show that there was normalization of some of the imaging findings after ERT, suggesting that while early brain lesions are common in IOPD, they may not necessarily progress. Additionally, several reports [20,23] describe deep white matter changes in CRIM-negative cases as early as 44 months of age. Most recently, Ebbink et al. reported MRI findings indicating periventricular white matter abnormalities in 10 classic infantile patients. In older patients, these abnormalities extended to subcortical areas, with some involvement of the capsula [21].

White matter abnormalities are observed in a wide range of other neurological and cognitive disorders, including metachromatic leukodystrophy, adrenoleukodystrophy, and other neonatal inborn errors of metabolism such as Fabry disease, Krabbe disease and mucopolisidosis [34,35]. Although it is clear that white matter abnormalities are seen in individuals with many different cognitive and learning deficits [36,37], an explicit relationship between white matter changes and impaired cognition has not been demonstrated.

In the case of IOPD, the finding of white matter changes is a concern. Importantly, our findings suggest that rather than exhibiting an overall intellectual disability, there may be underlying language-based learning deficits in some individuals with IOPD related to their below-average performance on academic tasks. Because of the specificity of these functions, as well their localization and circuitry within the brain, the connection between the physiology of the CNS and the cognitive outcome of IOPD individuals needs to be further characterized. Additional imaging technologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans may have the ability to more directly and dynamically correlate physiology to behavior. At this point, we are in an early stage of our understanding of white matter abnormalities in IOPD and cannot make definite conclusions about the neurophysiological underpinnings of learning deficits in children with IOPD.

Currently, therapies for IOPD largely focus on delivery to skeletal muscle and improvement in motor, pulmonary and cardiac function [1]. Still, long-term motor outcome in IOPD survivors does show residual motor deficit, which in some cases is significant. This may be due to the limitations of alglucosidase alfa and/or the later initiation of ERT in our sample. Earlier treatment may result in better motor outcomes and possibly better overall outcome as many of our measures are dependent on motor abilities. As we deepen our understanding of the neurocognitive profile and neurophysiological phenotype of long-term IOPD survivors, it becomes increasingly evident that there is a CNS component to the disease, underscoring the

need for treatment approaches that will target the cognitive and behavioral components as well.

Additionally, it is important to note that all reports of cognitive and academic development in IOPD thus far are of CRIM-positive individuals. A necessary next step is to understand the cognitive outcome in CRIM-negative survivors, as they represent the extreme phenotype in classic IOPD, falling at the most severe end of the IOPD spectrum.

Overall, our findings highlight the variability in the long-term cognitive outcomes of children with IOPD treated with ERT. At one end, there is a group of younger participants with nonverbal cognitive abilities in the average range and significantly lower academic skills. At the other end we have adolescents who exhibit average or above average cognitive and academic skills. It is critical that the cognitive and academic skills of children with IOPD be assessed yearly, as part of their routine care, to help detect a change in their overall status and potentially prevent a decline in their abilities. The test battery should include measures of cognitive, academic and language functioning that minimize each participants' areas of weakness. IQ tests should be selected and interpreted with care, considering each individual's motor skills, speech and language abilities, hearing status and native language. Standardizing measures across clinical/research groups would also be helpful. Ideally, testing sessions should be conducted early in the day for limited time periods to minimize fatigue, using the most appropriate measures for each individual child. It would also be useful to systematically assess the presence of attention, mood and behavioral issues. Our group is now including standardized behavioral checklists completed by the children's parents as part of the test battery. Continued follow-up by a multidisciplinary team is essential to better understand the neurocognitive profile of these remarkable children and the factors impacting their long-term outcome.

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Demographics and status of participants with infantile-onset Pompe disease at most recent psychological evaluation.

Table 1

Participant	Gender	Race/Ethnicity	Age at ERT start (months)	Age at most recent testing (years, months)	Ambulates independently (with/without AFOs)	Dysarthria	Hearing loss	Other
A	M	White	0.2	8,3	Yes	No	Yes	Hearing aids, glasses, ADHD & ASD diagnoses
B	F	White	6	10,10	No	Yes	No	Anxiety
C	M	White	2.9	12,1	No	Yes	Yes	Hearing aids, G-tube feedings, glasses, mood disorder
D	M	Hispanic	6	12,3	No	Yes	Yes	Hearing aids, contact lenses
E	F	Hispanic	4.9	13,4	No	Yes	Yes	Hearing aids (but does not routinely wear, glasses, G-tube feedings)
F	M	White	1.0	17,0	No	Yes	No	Contact lenses
G	M	Asian-Indian	3.1	15,3	Yes	Yes	Yes	Hearing aids recommended, but none currently
J	F	White	6.0	11,1	Yes	Yes	Yes	Hearing aids, glasses, anxiety
K	M	Jamaican	25.0	5,6	Yes	Hypernasal	No	ADHD
L	M	Middle Eastern	18 hours	9,0	Yes	Yes	Yes (in past)	Glasses
M	F	White	2.1	7,9	Yes	Yes	Yes	Hearing aids glasses

AFO = ankle-foot orthoses; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder.

Table 2

Participants’ educational placement and support services at most recent psychological evaluation.

Participant ID	Age at testing	Grade level	Classroom placement	IEP	Speech-language therapy	Occupational therapy	Physical therapy	Home-bound instruction
A	8,3	2nd	Self-contained EC classroom	Yes	School	School	No	None
B	10,10	5th	Regular classroom, with full-time paraprofessional	Yes	School	School	School & private	4,5 h/mo
C	12,1	6th	Homebound instruction (partially at home, partially at hospital)	Yes	School	School	School & private	8 h/mo
D	12,3	Rising 6 th	Self-contained EC classroom for academics, general education classroom for electives	Yes	School & home-based	No	School & home-based	None
E	13,4	8th	Self-contained EC classroom for most academics	Yes	No	No	Private	8 h/week
F	17,0	Rising 12 th	Regular classroom	Section 504 Plan ^a	No	No	No	None
G	15,3	10th	Regular classroom, private school	No	No	No	Private	Tutoring at home
J	11,1	5th	Self-contained EC classroom and regular classroom	Yes	School	School	School	None
K	5,6	Rising kindergarten	Regular classroom	Yes	School	No	No	None
L	9,0	3rd	Regular classroom with full-time paraprofessional	No	No	No	No	None
M	7,9	2nd	Regular classroom with full-time paraprofessional	Yes	School	School (consultation)	Private	None

EC = Exceptional Children; IEP = Individualized Education Program, which includes the specialized instruction and related services (such as physical therapy) that a child with an identified disability will receive in the public school setting.

^aSection 504 of the Rehabilitation Act ensures that a child with an identified disability receives appropriate accommodations in the public school setting (such as the use of elevators).

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Table 3
Full Scale IQs for the Wechsler scales (WPPSI, WISC, WAIS) and Nonverbal IQs for the Leiter scales over time.

ID	Age (Measure)	WPPSI-III	WPPSI-IV	WISC-IV	WISC-V	WAIS-IV	Leiter-R ^a	Leiter-3
A	4,11 (WPPSI-III)^a	73						
	6,6 (WPPSI-III)	73						
	8,3 (WISC-IV; Leiter-3)		68					88
B	5,6 (WPPSI-III)^a	83						
	6,11 (WISC-IV)		87					
	8,7 (WISC-IV)		75					
	9,8 (WISC-V; Leiter-3)			72	80			84
C	10,10 (WISC-V; Leiter-3)							75
	6,7 (WISC-IV)^a		83					
	8,11 (WISC-IV)		68					
	10,11 (WISC-V)			66				
	11,0 (Leiter-3)							87
D	12,1 (WISC-V; Leiter 3)			60				99
	8,0 (Leiter-R)^a					85		
	10,1 (Leiter-R)					87		
E	12,3 (Leiter-3)							97
	7,10 (Leiter-R)^a					80		
	9,0 (Leiter-R)					73		
F	13,4 (Leiter-3)							96
	7,1 (WISC-IV)^a		96					
	14,1 (WISC-IV)		107					
G	16,0 (WAIS-IV)					110		
	17,0 (WAIS-IV)					116		
	8,11 (WISC-IV)^a		109					
	12,4 (WISC-IV)		123					
	15,3 (WISC-V)		110					

ID	Age (Measure)	WPPSI-III	WPPSI-IV	WISC-IV	WISC-V	WAIS-IV	Leiter-R ^a	Leiter-3
J	8,3 (WISC-IV)			74				
	11,1 (WISC-IV)			51				
K	5,6 (WPPSI-IV)		105					
L	6,1 (Leiter-3)						77	
	7,9 (Leiter-3)						67	
	9,0 (Leiter-3)						69	
M	4,0 (WPPSI-IV)		94					
	5,3 (WPPSI-IV)		89					
	7,9 (WISC-V)			88				

The Brief Nonverbal IQ (NVIQ) is reported for the Leiter-R, which is comprised of 4 subtests for all ages: Figure Ground, Form Completion, Sequential Order, and Repeated Patterns. The Brief NVIQ was selected as it more closely matches the NVIQ from the Leiter-3, which is comprised of 4 subtests for all ages: Figure Ground, Form Completion, Sequential Order, and Classifications and Analogies.

All IQ scores are standard scores, with a mean of 100 and a standard deviation of 15.

^aData from these test administrations were first reported in Spiridigliozzi et al. [11].

Table 4

Most recent standard scores for Wechsler Full Scale IQs, Leiter Nonverbal IQs and Woodcock-Johnson academic skill subtest scores and Composite scores for all participants.

ID	Age (Measure)	Full Scale IQ (FSIQ)	Nonverbal IQ (NVIQ)	WJ Letter-Word Identification	WJ Passage Comprehension	WJ (Sentence) Reading Fluency	WJ Broad Reading	WJ Spelling	WJ Writing Samples	WJ (Sentence) Writing Fluency	WJ Broad Written Language	WJ Calculation	WJ Applied Problems	WJ Math (Facts) Fluency	WJ Broad Mathematics	Academic Fluency
K	5,6 (WPPSI-IV; no WJ)	105														
M	7,9 (WISC-V; WJ-IV)	88		97	92	88	91	82	108	95	94	94	85	101	94	93
A	8,3 (WISC-IV; Leiter-3; WJ-III)	68	88	68	58	M	60*	62	37	M	48*	54	73	M	62*	M
L	9,0 (Leiter-3; WJ-IV)		69	<40	<40	M				M			<40	M		M
B	10,10 (WISC-V; Leiter-3); 10,11 (WJ-IV)	80	75	96	83	89	89	96	108	101	101	102	87	107	99	97
J	11,1 (WISC-IV; no WJ)	51														
C	12,1 (WISC-V; Leiter-3); 12,2 (WJ-IV)	60	99	<40	<40	<40	< 40	<40	<40	41	< 40	59	67	53	52	< 40
D	12,3 (Leiter-3; WJ-IV)		97	50	<40	52	42	55	67	77	58	54	84	65	61	55
E	13,4 (Leiter-3; WJ-IV)		96	64	50	81	66	73	92	90	80	52	53	80	56	80
G	15,3 (WISC-V; WJ-IV)	110		114	105	110	112	117	111	109	117	93	123	101	106	108
F	17,0 (WAIS-IV; WJ-IV)	116		107	126	115	120	106	123	100	113	115	107	112	114	114
M _{age} = 11.1; Median _{age} = 11.1; SD _{age} = 3.4																
Mean		84.8	87.3	74.9	70.1	82.0	77.4	78.8	85.6	87.6	81.3	77.9	79.8	88.4	80.5	83.7
Median		84.0	92.0	68.0	58.0	88.0	77.5	77.5	100.0	95.0	87.0	76.0	84.0	101.0	78.0	93.0
SD		24.2	12.6	29.3	32.5	28.0	30.5	26.7	33.7	22.9	29.9	25.7	25.7	22.7	25.2	27.7

The Broad Reading composite is comprised of the following subtests: Letter-Word Identification, Passage Comprehension, and Sentence Reading Fluency. The Broad Written Language composite is comprised of the following subtests : Spelling, Writing Samples, and Writing Fluency. The Broad Mathematics composite is comprised of the following subtests: Calculation, Applied Problems, and Math Fluency. Scores marked with a subscript M (M_j) are missing (i.e., subtest was not administered). Scores marked with an asterisk (*) are Brief composite scores, which are comprised of 2 (not 3) subtests, and include: Brief Reading, Brief Writing, and Brief Math.

All IQ and WJ subtest and composite scores are standard scores, with a mean of 100 and a standard deviation of 15. IQ and WJ composite scores are bolded.

Table 5

Most recent standard scores for Wechsler Full Scale IQs, Leiter Nonverbal IQs and Woodcock-Johnson academic skill subtest scores and Composite scores for below average performing and average performing subgroups.

Below average performing subgroup													
ID	Age (Measure)	Full Scale IQ (FSIQ)	Nonverbal IQ (NVIQ)	WJ Letter-Word Identification	WJ Passage Comprehension	WJ (Sentence) Reading Fluency	WJ Broad Reading	WJ Spelling	WJ Writing Samples	WJ (Sentence) Writing Fluency	WJ Broad Written Language	WJ Calculation	WJ Applied Problems
A	8,3 (WISC-IV; Leiter-3; WJ-III)	68	88	68	58	M	60*	62	37	M	48*	54	73
L	9,0 (Leiter-3; WJ-IV)		69	<40	<40	M				M		<40	
J	11,1 (WISC-IV; no WJ)	51											
C	12,1 (WISC-V; Leiter-3); 12,2 (WJ-IV)	60	99	<40	<40	<40	<40	<40	<40	41	<40	59	67
D	12,3 (Leiter-3; WJ-IV)		97	50	<40	52	42	55	67	77	58	54	84
E	13,4 (Leiter-3; WJ-IV)		96	64	50	81	66	73	92	90	80	52	53
Age	11.0 Mean	59.7	89.8	52.0	45.0	57.3	51.8	57.3	58.8	69.3	56.3	54.8	63.2
	11.6 Median	60.0	96.0	50.0	39.0	52.0	51.0	58.5	53.0	77.0	53.0	54.0	67.0
	2.0 SD	8.5	12.4	13.6	8.7	21.5	13.3	14.2	26.1	25.4	17.6	3.0	17.6
Average performing subgroup													
ID	Age (Measure)	Full Scale IQ (FSIQ)	Nonverbal IQ	WJ Letter-Word Identification	WJ Passage Comprehension	WJ (Sentence) Reading Fluency	WJ Broad Reading	WJ Spelling	WJ Writing Samples	WJ (Sentence) Writing Fluency	WJ Broad Written Language	WJ Calculation	WJ Applied Problems
K	5,6 (WPPSI-IV; no WJ)	105											
M	7,9 (WISC-V; WJ-IV)	88		97	92	88	91	82	108	95	94	94	85
B	10,10 (WISC-V; Leiter-3); 10,11 (WJ-IV)	80	75	96	83	89	89	96	108	101	101	102	87
G	15,3 (WISC-V; WJ-IV)	110		114	105	110	112	117	111	109	117	93	123
F	17,0 (WAIS-IV; WJ-IV)	116		107	126	115	120	106	123	100	113	115	107
Age	11.3 Mean	99.8	75.0	103.5	101.5	100.5	103.3	100.3	112.5	101.3	106.3	101.0	100.5
	10.8 Median	105.0	75.0	102.0	98.5	99.5	101.5	101.0	109.5	100.5	107.0	98.0	97.0
	4.9 SD	15.2		8.6	18.7	14.0	15.4	14.9	7.1	5.8	10.6	10.2	18.0

All IQ and and WJ subtest and composite scores are standard scores, with a mean of 100 and a standard deviation of 15. Scores marked with an asterisk (*) are Brief composite scores, which are comprised of 2 (not3) subtests, and include: Brief Reading, Brief Writing, and Brief Math. IQ and WJ composite scores are bolded.

Table 6
Most recent Wechsler Full Scale IQs and Composite scores and Leiter Nonverbal IQ scores.

ID	Age (Measure)	Verbal Comprehension	Perceptual Reasoning	Visual Spatial	Fluid Reasoning	Working Memory	Processing Speed	Full Scale IQ (FSIQ)	Nonverbal IQ (NVIQ)
K	5,6 (WPPSI-IV)	90		94	127	118	100	105	
M	7,9 (WISC-V)	92		94	82	97	92	88	
A	8,3 (WISC-IV; Leiter-3)	69	73			74	80	68	88
L	9,0 (Leiter-3)								69
B	10,10(WISC-V; Leiter-3)	89		69	79	107	86	80	75
J	11,1 (WISC-IV)	74	47			65	53	51	
C	12,1 (WISC-V; Leiter 3)	59		67	69	69	69	60	99
D	12,3 (Leiter-3)								97
E	13,4 (Leiter-3)								96
G	15,3 (WISC-V)	108		102	121	122	89	110	
F	17,0 (WAIS-IV)	134	111			111	92	116	

The Brief Nonverbal IQ (NVIQ) is reported for the Leiter-R, which is comprised of 4 subtests for all ages: Figure Ground, Form Completion, Sequential Order, and Repeated Patterns. The Brief NVIQ was selected as it more closely matches the NVIQ from the Leiter-3, which is comprised of 4 subtests for all ages: Figure Ground, Form Completion, Sequential Order, and Classifications and Analogies.

All IQ and composite scores are standard scores, with a mean of 100 and a standard deviation of 15. Wechsler Full Scale IQs and Leiter Nonverbal IQs are bolded.

Table 7

Beery-Buktenica Visual Motor Integration (VMI) 5th and 6th edition, subtest standard scores.

ID	Age	VMI	Visual Perception	Motor Coordination
A	6,6	84	46	91
	8,3	69	81	86
B	6,11	82	74	76
	8,7	73	98	78
	9,8	76	91	56
C	10,11	45	73	60
D	10,1	75	82	55
	12,3	72	52	45
E	9,0	79	69	72
F	14,1	83	101	98
	16,0	100	89	98
G	12,4	100	84	73
J	8,4	69	77	78
	11,1	52	58	<45
K	5,6	<i>100^a</i>	<i>95^a</i>	<i>56^a</i>
L	7,9	66	45	54
	9,0	48	< 45	<45
M	4,0	<i>100^b</i>	<i>74^b</i>	<i>88^b</i>
	5,3	94	90	93
	7,9	81	74	84
Mean	10.2	<i>74.7</i>	<i>73.6</i>	<i>65.3</i>
Median	9.7	<i>76.0</i>	<i>74.0</i>	<i>60.0</i>
SD	2.8	<i>20.3</i>	<i>16.6</i>	<i>18.6</i>

All of the VMI scores are from the VMI 6th edition, with the exception of those in italics and marked with an asterisk (*), which are from the VMI 5th edition.

Mean, Median, and SD were calculated for the most recent administration.