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 subgroups emerged based on participants’ average or below average performance on the majority of academic subtests. Those participants with below average academic skills (n = 6) demonstrated average nonverbal cognitive abilities on the Wechsler scales and less medical involvement. Their speech and language skills appeared to be more intact. However, both groups earned average or below average 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 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 participants. 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 average or 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.

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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 outcome for improved survival. The availability of ERT has led to a decrease in mortality and an increase in long-term ventilator-free survival in IOPD survivors. However, long-term survival and cognitive outcomes of IOPD survivors remain unclear.

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 subgroups emerged based on participants’ average or below average performance on the majority of academic subtests. Those participants with below average academic skills (n = 6) demonstrated average nonverbal cognitive abilities on the Wechsler scales and less medical involvement. Their speech and language skills appeared to be more intact. However, both groups earned average or 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.

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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, Third Edition (BSID-III) [7], within signiﬁcant cognitive development on the Bayley Scales of Infant and Toddler 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
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