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Neuroimaging Findings in Infantile Pompe Patients Treated with Enzyme Replacement Therapy

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Abstract

Background—Recombinant human acid α-glucosidase (rhGAA) enzyme replacement therapy (ERT) has prolonged survival in infantile Pompe disease (IPD), but has unmasked central nervous system (CNS) changes.

Methods—Brain imaging, consisting of computed tomography (CT) and/or magnetic resonance imaging (MRI), was performed on 23 patients with IPD (17 CRIM-positive, 6 CRIM-negative) aged 2–38 months. Most patients had baseline neuroimaging performed prior to the initiation of ERT. Follow-up neuroimaging was performed in eight.

Results—Sixteen patients (70%) had neuroimaging abnormalities consisting of ventricular enlargement (VE) and/or extra-axial cerebrospinal fluid accumulation (EACSF) at baseline, with delayed myelination in two. Follow-up neuroimaging (n=8) after 6–153 months showed marked improvement, with normalization of VE and EACSF in seven patients. Two of three patients imaged after age 10 years demonstrated white matter changes, with one noted to have a basilar artery aneurysm.

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Conflict of interest disclosures:

PSK has received research/grant support and honoraria from Genzyme Corporation and Amicus Therapeutics. PSK is a member of the Pompe and Gaucher Disease Registry Advisory Board for Genzyme Corporation. LDH has received research/grant support and honoraria from Genzyme, a Sanofi Company. LDH has also received a consultant fee for Wiley for role as Associate Editor of Muscle & Nerve. PM has received speaker honorarium from Genzyme as a participant in Genzyme's Patient Speakers Bureau. ZBK, SP, SB, SA, RW, DE and DF do not have conflicts to disclose.

Ethics approval and consent to participate

Written informed consent was obtained from a parent or guardian for all individuals as part of Duke Institutional Review Board approved Pompe long-term follow-up study (Pro00010830) and/or Determination of CRIM status in Pompe disease (Pro00001562).

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Conclusions—Mild abnormalities on brain imaging in untreated or newly treated patients with IPD tend to resolve with time, in conjunction with ERT. However, white matter changes are emerging as seen in Patient 1 and 3 which included abnormal periventricular white matter changes with subtle signal abnormalities in the basal ganglia and minimal, symmetric signal abnormalities involving the deep frontoparietal cerebral white matter, respectively. The role of neuroimaging as part of the clinical evaluation of IPD needs to be considered to assess for white matter changes and cerebral aneurysms.

Keywords

Pompe disease; glycogen storage disease type II; neuromuscular diseases; neuroimaging; central nervous system; blood-brain barrier; enzyme replacement therapy; MRI; CT; rhGAA; alglucosidase alfa; acid maltase deficiency

2. INTRODUCTION

Pompe disease, also known as glycogen storage disease type II (GSD II), is a lysosomal storage disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (GAA). Classic infantile Pompe disease (IPD) presents within the first days to weeks of life, is rapidly progressive, and is characterized by severe cardiomyopathy, respiratory failure, and death typically within the first two years of life [1–3]. Non-classic IPD presents in the first year of life with less severe cardiomyopathy, but significant muscle weakness and usually leads to respiratory failure by early childhood in untreated patients.

Excess glycogen accumulates in the lysosomes of multiple tissues, including skeletal, cardiac, and smooth muscles [4]. Central nervous system (CNS) glycogen deposition has been reported in neurons of the cerebral cortex, brainstem, and anterior horn of the spinal cord, as well as in glial cells of the cerebral cortex and Purkinje cells of the cerebellum [4–9]. In the peripheral nervous system (PNS), neuronal glycogen storage has been found in the dorsal root ganglia, myenteric plexus neurons, and within the cytoplasm of Schwann cells comprising peripheral nerves [8, 10]. Glycogen deposition has also been described in parasympathetic and truncospinal neurons as well as in intracranial vessels, most prominent in cerebral capillaries, basilar arteries, and the choroid plexus [11–13].

In 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa©; Myozyme©, Lumizyme©, Genzyme Corporation, Cambridge, MA) was approved as the first treatment for patients with Pompe disease. For the majority of patients, treatment with rhGAA has led to prolonged survival and improved quality of life [7, 8, 14]. Concurrent with prolonged patient survival, ERT has revealed aspects of IPD previously not seen secondary to early demise, including the unmasking of CNS disease.

While it has become increasingly possible to understand how IPD affects less-well characterized organ systems, including the CNS, much of the existing literature is based upon scattered autopsy reports and small case series [3, 8, 15–24]. Brain magnetic resonance imaging (MRI) and computed tomography (CT) might serve as non-invasive alternatives for testing. The purpose of this investigation is to describe the baseline neuroimaging findings of 23 patients with classic (n=22) and non-classic (n=1) IPD and long-term follow-up on

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neuroimaging findings in eight of these 23 patients treated with rhGAA. Three patients were followed through 10 years of age.

3. SUBJECTS AND METHODS

The Duke Institutional Review Board approved this retrospective study of twenty-three patients evaluated between 1999–2015 who had undergone brain imaging with CT or MRI as part of clinical care. All patients had a confirmed diagnosis of Pompe disease with <1% of the normal mean GAA activity in skin fibroblasts and *GAA* mutation analysis according to previously published methods [14]. Cross-reactive immunologic material (CRIM) status was determined as described previously using a pool of monoclonal antibodies that recognize both native and recombinant GAA and by genetic mutation analysis [14].

Experienced subspecialty board-certified neuroradiologists evaluated each scan. One individual (DSE), a board-certified neuroradiologist with over 20 years of subspecialty experience, retrospectively reviewed the neuroimaging studies of all 23 patients while blinded to their clinical information. His opinion was considered final in any instances of discrepancy. Head circumference (HC) and other growth parameters were measured at baseline and upon follow-up neuroimaging as part of the routine clinic visits.

4. RESULTS

In this cohort of 23 patients with IPD (17 CRIM-positive, 6 CRIM-negative), the median age at ERT initiation was 7 months (range: 2.4 - 37.8 months) (Table 1). Twenty-two (96%) received either 20 mg/kg (n = 20) or 40 mg/kg (n = 2) of rhGAA every other week. One patient (Patient 14) had baseline neuroimaging but died prior to starting ERT. Twenty-two (96%) were normocephalic at baseline, defined as having an age-adjusted head circumference (HC) between the 10^{th} and 90^{th} percentiles (median 25^{th} percentile). A single patient had microcephaly with a HC in the 3^{rd} percentile. HC at second study ranged from the 25^{th}-90^{th} percentiles (median 50^{th} percentile; n = 7) and at third study ranged from the 15^{th}-90^{th} percentiles (median 50^{th} percentile; n = 4) (Table 2). No discrepancy was found between HC and other growth parameters.

Baseline brain imaging

Eighteen IPD patients had baseline head CT evaluations and five IPD patients had baseline brain MRI. Neuroimaging exams were correlated with HC. The majority of patients (18; 78%) had baseline neuroimaging performed prior to initiation of ERT. The other five patients had baseline neuroimaging at an average of 15 weeks (range 2 - 24.4 weeks) after the start of ERT. Baseline studies were normal in seven (30%) patients (CT: 5 patients, MRI: 2 patients) without evidence of lateral ventricular enlargement (VE), extra-axial cerebrospinal fluid accumulation (EACSF), or other CNS abnormalities. The baseline studies of the remaining 16 patients (70%) demonstrated VE and/or EACSF. Thirteen had both VE and EACSF, one had VE without EACSF, and two had EACSF without VE. Of the five patients who had MRI at baseline (mean age 16.4 months), a global delay in myelination was observed in two patients (40%; Patient 5 [CRIM-positive] and Patient 14 [CRIM-negative]).

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Follow-up brain imaging

Follow-up neuroimaging consisting of head CT and/or brain MRI were performed in eight patients (7 CRIM-positive [Patients 1, 2, 3, 4, 5, 7, and 8], 1 CRIM-negative [Patient 6]), as clinically indicated per the treating physician. The average age at baseline study for these eight patients was 5 months (range 2 – 9 months), with the results of all follow-up studies summarized in Table 2.

A second neuroimaging study was performed in eight patients (CT: 2 patients [Patients 1 and 2], MRI: 6 patients [Patients 3, 4, 5, 6, 7, and 8]) ranging in age from 9 to 71 months (mean 25 months). The interval between baseline and second study scans was 6 to 69 months (mean 20 months). Seven of eight patients (88%; Patients 1, 2, 3, 4, 5, 6, and 7) demonstrated VE and/or EACSF upon baseline neuroimaging. Of the seven with abnormal baseline studies, five (71%; Patients 1, 2, 3, 5, and 7) demonstrated normalization at follow-up (see Figure 1 for a representative image). The two patients (Patients 4 and 6) who continued to demonstrate CNS abnormalities on follow-up imaging showed stabilization of their VE and/or EACSF. The lone patient (Patient 8) with normal baseline imaging at age 2 months did not develop any abnormalities on follow-up imaging at age 71 months. Of the six patients with MRI at second study (mean age 28.3 months), only one (Patient 5) had a delay in myelination status upon neuroimaging performed at 50 months. However, his myelination status demonstrated significant interval improvement from his baseline MRI scan at 9 months, with only residual delayed myelination (Figure 2). None of the six patients with MRI at second study had other signs of white matter abnormalities.

A third study (MRI) was performed on four CRIM-positive patients (Patients 1, 2, 3, and 4) ranging in age from 24 to 64 months (mean 41 months), with an interval between the second and third study of 12 to 49 months (mean 26 months). All had normal findings on MRI with resolution of previously noted VE and/or EACSF; therefore, six of seven patients (86%; Patients 1, 2, 3, 4, 5, and 7) with baseline VE and/or EACSF had resolution of these findings.

A fourth study (MRI) was performed on three CRIM-positive patients (Patients 1, 3, and 4) at a mean age of 138 months (11.5 years). Patient 1’s fourth study, performed at age 13 years, revealed diffuse abnormal periventricular white matter changes with subtle signal abnormalities in the basal ganglia (Figure 3). Patient 3’s fourth study occurred at age 11.5 years. While the two prior MRI studies (at ages 1 year and 2 years) had been normal, this study demonstrated minimal, symmetric signal abnormalities involving the deep frontoparietal cerebral white matter. Of note, a magnetic resonance angiography (MRA) performed on Patient 3 at age 9 years revealed a basilar aneurysm but was not reviewed as part of this study [25]. Patient 4 had a normal brain MRI at age 10 years.

With regards to our cohort of six patients with CRIM-negative IPD, four (67%) had VE and/or EACSF upon baseline study at a mean age of 10 months (range 2.5 – 38 months) compared to 12 of our 17 CRIM-positive patients (71%) having VE and/or EACSF upon baseline study at a mean age of 9.9 months (range 2 – 37 months). Only one CRIM-negative patient (Patient 14) had a baseline MRI, which showed a global delay in myelination at age 38 months. Patient 6 was the only CRIM-negative patient with follow-up neuroimaging.

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Both the baseline CT at 3 months and the follow-up MRI at 9 months revealed VE and EACSF. The MRI at 9 months did not demonstrate hypomyelination or other white matter abnormalities.

5. DISCUSSION

In this retrospective study of 23 patients with IPD, 70% were found to have VE and/or EACSF at baseline imaging study regardless of CRIM status. These abnormalities in untreated or newly treated patients tended to resolve with time and ERT (6 of 7; 86%). However, as infantile Pompe survivors reached late childhood and early adolescence, they appeared to be at risk of developing white matter abnormalities as seen in two of our three patients imaged after the age of 10. Cerebral aneurysms as noted in an MRA study done on Patient 3 was also noted at age of 9 years.

This study expands upon the current understanding of CNS involvement in IPD. The key findings of previously published case series are summarized in Table 3. Our study and prior publications demonstrate that it is not uncommon for young patients with IPD to demonstrate VE, EACSF, and delayed myelination. As IPD survivors age into late childhood, the structural abnormalities of VE and EACSF tend to resolve, yet white matter changes are noted. Children with both CRIM-negative and CRIM-positive IPD are at risk for developing white matter signal hyperintensities (WMH) on MRI, as seen in our study and reported by others (see Table 3 for details). The WMH are reported in the deep white matter with involvement extending into the subcortical white matter with sparing of the U-fibers [19, 23].

In our cohort WMH appeared in the follow up studies done on two patients (Patients 1 and 3), at ages 13 and 11.5 years, respectively. The majority of cases reported with white matter abnormalities have been older IPD survivors, yet there are reports in children as young as 18 months [17, 19–22]. In this study WMH were seen in CRIM-positive cases, .CRIM-negative cases in this series died despite ERT as this was in the era prior to immune modulation, which has significantly changed the clinical outcome of CRIM negative IPD. The only CRIM-negative patient with a follow-up imaging data in this study was Patient 6.who had baseline and follow-up neuroimaging performed at 3 and 6 months of age respectively. Since the addition of immune modulation as part fo treatment algorithm CRIM-negative patients are now living longer, which will provide the ability to evaluate these cases. There is limited imaging data on CRIM-negative cases as described by the case reports of Messinger *et al.* and Rohrback *et al* [19, 20]

The underlying etiology of VE and EACSF accumulation is not well characterized in non-traumatic presentations, including IPD. These abnormalities are often associated with hydrocephalus and increased head circumference, but this was not seen in our cohort. While EACSF and VE may be transient normal findings, it was observed in 70% of our cohort at baseline study. “Benign” EACSF and VE due to immature arachnoid granulations are associated with increased or upper normal HC. A differing etiology in our IPD patients is strongly supported by the low normal HC pretreatment with relative increased HC exceeding normal HC curve trends following initiation of ERT.

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Possible explanations for VE and EACSF in IPD do exist. Cerebrospinal fluid (CSF) accumulation is generally thought to arise from over-secretion and/or decreased absorption of CSF. Autopsy findings from patients with IPD have shown an accumulation of glycogen in pericytes of capillaries, possibly resulting in a weakening of the vascular wall and thus vascular leakage and decreased absorption of CSF [8]. Glycogen deposition has also been reported in intracranial vessels, including the basilar artery and cerebral capillaries [13, 17]. Pompe-associated glycogen accumulation in vascular smooth muscle cells adjacent to endothelial tight junctions may block endothelial fenestrations, thus impeding the normal passage of CSF. This would result in CSF accumulation in the lateral ventricles, although hydrocephalus although reported in one IPD patient [16] and one late-onset Pompe disease [26] is usually not associated with Pompe disease. An alternative hypothesis is that the brain parenchyma is relatively slower to develop in IPD and the resultant relative decreased volume may manifest as increased ventricular size and EACSF. As ERT normalizes the effects of Pompe disease, the brain matures and normalizes its appearance subsequent to therapy.

Chien *et al.* speculated that a small amount of enzyme (dosed at 20 mg/kg every 2 weeks) may penetrate the blood brain barrier (BBB) [17]. Begley *et al.*, however, proposed that an increased load of enzyme does not necessarily lead to increased CNS enzyme delivery. Rather, exposure of the BBB to high levels of enzyme for periods up to two weeks might reactivate a mannose-6-phosphate receptor dependent receptor mediated transcytosis [27]. It has also been proposed the structural integrity and function of the BBB may be compromised in Pompe disease by the accumulation of glycogen in the vascular smooth muscle cells or as a secondary event following microglial activation and associated inflammatory cascades, resulting in increased permeability of the BBB [28, 29]. Thus, the white matter abnormalities seen on MRI may be attributable to increased water content in the white matter secondary to an abnormal BBB rather than abnormal myelination. Increased water content resulting from a disrupted BBB is one hypothesized cause for the leukodystrophic MRI findings in another congenital disease of the muscles, merosin deficient congenital muscular dystrophy [30].

The impact of CNS glycogen accumulation in IPD is poorly understood at this time, and effects on cognitive development remain unclear. In concert with recent studies on cognitive function in children with IPD [21, 23, 31, 32], we speculate that the decreased processing speeds seen in IPD long-term survivors could be secondary to glycogen storage within the CNS, possibly correlating to abnormalities seen on neuroimaging studies. In our current series, four children (17%) had concerns for non-motor delay at time of last clinic follow-up based on review of clinic notes (information not included). It is difficult to analyze this information as the current data from this retrospective study are limited by a lack of formal cognitive testing, including IQ assessment, performed at the time of repeat imaging. Furthermore, several children included in the study died at a young age, before cognitive delays could be properly assessed in clinic. Prospective studies examining the relationship between neurocognitive testing and neuroimaging findings will aid our understanding of the CNS and cognitive effects seen in long-term survivors of IPD.

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The current retrospective study does have its limitations, including a small sample size with 23 patients with baseline neuroimaging and eight patients with follow-up studies. Although considered small, it represents the largest series published to date in this rare disease. Our institution is a Pompe disease center, evaluating and caring for patients from a broad national and international referral base, including accompanying imaging studies, making standardized imaging difficult. The inability to have all images performed at a single location was addressed by having a single, experienced neuroradiologist review all the imaging studies while blinded to clinical status. As this study was a retrospective chart review of the patients who already had either CT/MRI performed clinically, there may be a potential selection bias of patients who were doing worse neurologically. While baseline MRI of the brain would have been preferable to assess myelination, sedating infants would have been an unacceptable risk. Sedation risk is high in IPD due to underlying respiratory weakness and cardiomyopathy. With improvements on ERT, sedation and anesthesia risks decrease substantially [33].

In conclusion, early findings of VE, EACSF, and delayed myelination in IPD should not be cause for alarm. Routine clinical imaging to assess for these findings to date has not been recommended for infants and young children, although CT and MRI of the brain are sometimes ordered as part of the diagnostic evaluation. Regular brain imaging as a part of routine surveillance as these IPD children grow older will shed more light on the age at which the white matter changes are first noted and its progression. MRI and MRA of the brain should be considered in the evaluation of children with Pompe disease to assess for both white matter disease and cerebral aneurysms given the growing body of literature of these CNS findings. Larger prospective studies are needed to allow recommendations on neuroimaging frequency in survivors of IPD. As the phenotype of treated disease unfolds, longitudinal studies must be performed to correlate developmental, neurological, and cognitive findings with the presence of neuroimaging abnormalities. These findings also raise the question of long-term effects on the CNS and the potential role of therapies that target the CNS.

6. Conclusion

Mild abnormalities on brain imaging in untreated or newly treated patients with IPD tend to resolve with time, in conjunction with ERT. However, white matter changes are emerging as seen in Patient 1 and 3 which included abnormal periventricular white matter changes with subtle signal abnormalities in the basal ganglia and minimal, symmetric signal abnormalities involving the deep frontoparietal cerebral white matter, respectively. The role of neuroimaging as part of the clinical evaluation of IPD needs to be considered to assess for white matter changes and cerebral aneurysms.

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List of abbreviations

rhGAA	Recombinant human acid α-glucosidase
ERT	enzyme replacement therapy
IPD	infantile Pompe disease
CNS	central nervous system
CT	computed tomography
MRI	magnetic resonance imaging
CRIM	cross reactive immunological material
VE	ventricular enlargement
EACSF	extra-axial cerebrospinal fluid accumulation
HC	head circumference
WMH	white matter signal hyperintensities
CSF	cerebrospinal fluid
BBB	blood brain barrier
RDCRN	Rare disease clinical research network
ORDR	Office of rare disease research
NCATS	National center for advancing translational science
NINDS	National institute of neurological disorders and stroke
NIDDK	National institute of diabetes and digestive and kidney diseases

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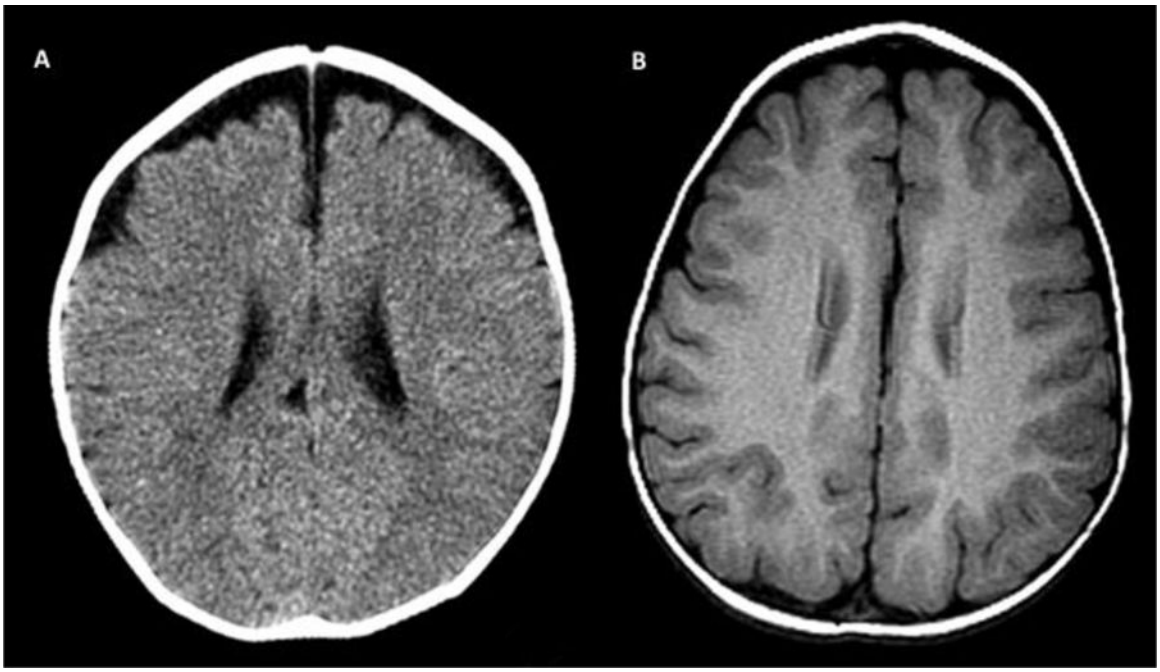

Figure 1.

(A) Axial head CT in a 6.5-month-old male (Patient 7) at the level of the upper ventricles is notable for prominent bifrontal extra-axial CSF spaces and mild prominence of the lateral ventricles. (B) Axial T1-weighted brain MRI of the same patient at 13 months of age (6 months into ERT) shows normalization of bifrontal extra-axial spaces and lateral ventricles.

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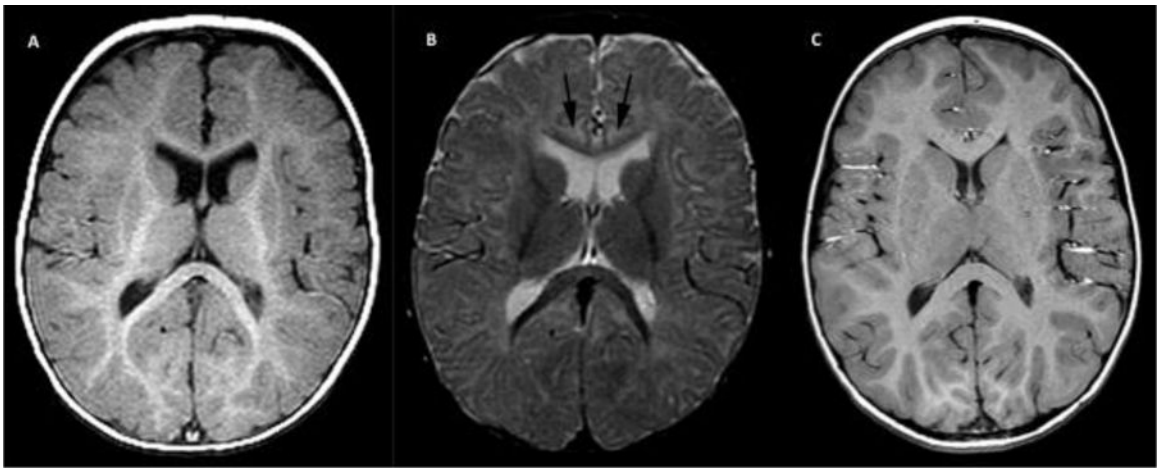

Figure 2.

(A) Baseline axial T1-weighted brain MRI in a 9-month-old male (Patient 5) demonstrates mild enlargement of the lateral ventricles and mild prominence of the bifrontal extra-axial CSF spaces in addition to incomplete myelination of the genu of the corpus collosum and relatively reduced subcortical white matter; (B) corresponding baseline T2-weighted image shows decreased white matter and mild delay in myelination of the genu of the corpus callosum (arrows). (C) Follow-up axial T1-weighted brain MRI of the same child obtained at 50 months of age (47 months into ERT) demonstrates normalization of the ventricles and extra-axial CSF spaces. There was significant interval progression of myelination with only residual delayed myelination seen on the follow-up study.

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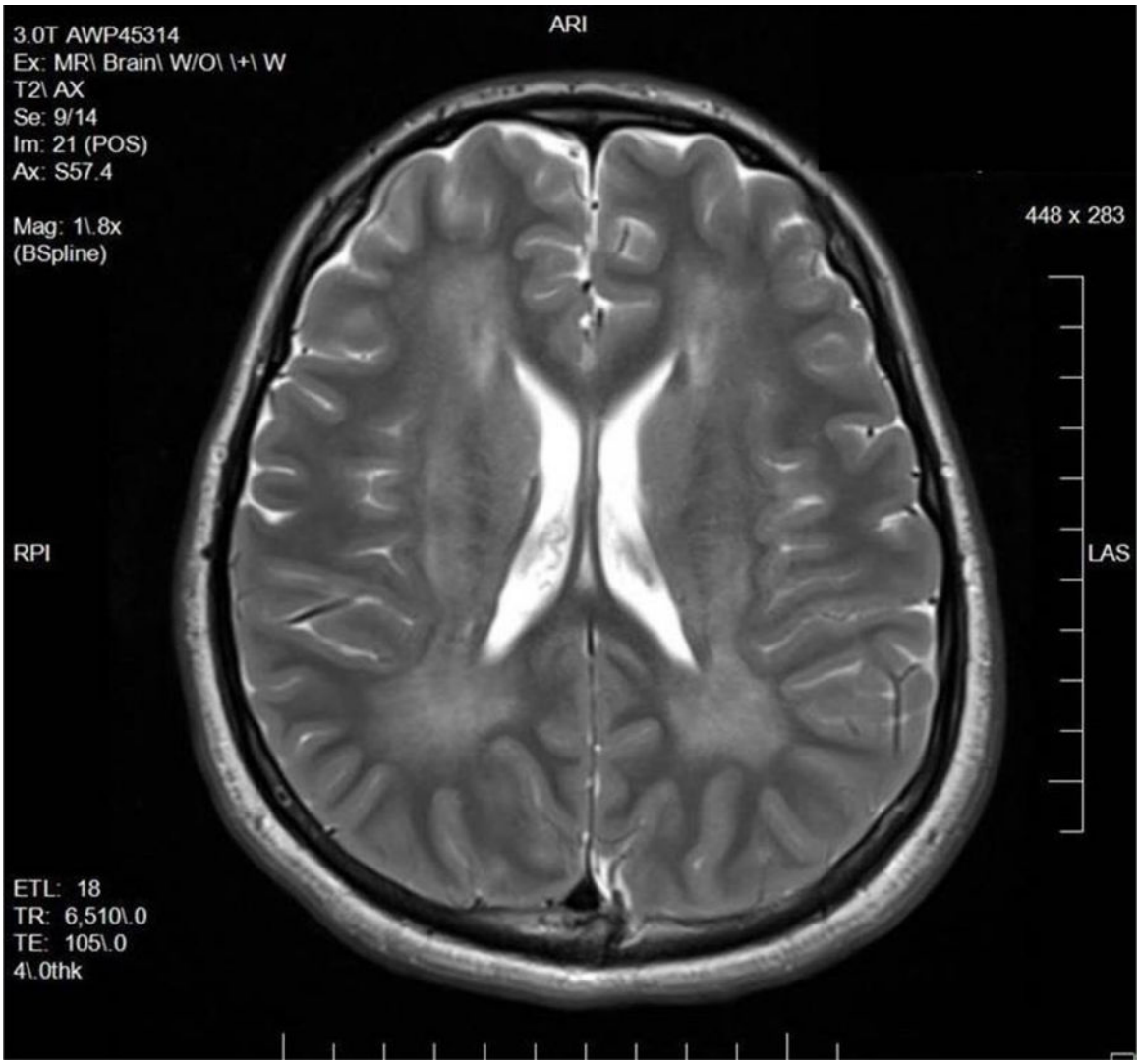

Figure 3.

Axial T2-weighted brain MRI in a 158-month-old (13.2 years) male (Patient 1) showing diffuse increased signal intensity periventricular white matter changes.

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Table 1

Baseline neuroimaging findings and demographic data of our cohort of 23 patients with infantile Pompe disease

Pt.	Sex	Age at First ERT (mo)	Age at Baseline Study (mo)	Head Circumference (percentile)	Modality	Ventricular Enlargement (VE)	EACSF	CRIM Status
1	M	4.7	4.5	41 cm (10^{th})	CT	(+)	(+)	positive
2	M	3.1	3	38.5 cm (10^{th})	CT	NL	(+)	positive
3	F	5.4	5	42.3 cm (50–75^{th})	CT	(+)	(+)	positive
4[a]	M	7.4	6	43.1 cm (25^{th})	CT	(+)	(+)	positive
5	M	2.9	9	44.5 cm (25^{th})	MRI	(+)	(+)	positive
6	F	3.7	3	39.5 cm (50^{th})	CT	(+)	(+)	*negative*
7[a]	M	7.0	6.5	43.5 cm (50^{th})	CT	(+)	(+)	positive
8	M	2.4	2	39.5 cm (50^{th})	CT	NL	NL	positive
9	M	4.2	4	39.7 cm (5^{th})	CT	NL	NL	*negative*
10	M	2.9	2.5	39.5 cm (25^{th})	CT	NL	NL	*negative*
11[b]	M	4.8	4.7	41 cm (25^{th})	CT	(+)	NL	*negative*
12	M	8.1	8	45 cm (50^{th})	CT	(+)	(+)	positive
13	F	8.5	8	41 cm (10^{th})	CT	NL	(+)	positive
14[c]	F	N/A	38	44 cm (90^{th})	MRI	(+)	(+)	*negative*
15[d]	M	37.8	37	52 cm (90^{th})	CT	(+)	(+)	positive
16	F	8.3	8	40 cm (3^{rd})	CT	(+)	(+)	*negative*
17	M	10.0	10	44.2 cm (10^{th})	CT	NL	NL	positive
18	M	18.3	18	49.1 cm (90^{th})	CT	(+)	(+)	positive
19	M	5.6	10	42.5 cm (5^{th})	MRI	(+)	(+)	positive
20	M	8.0	10	44.5 cm (10–25^{th})	CT	(+)	(+)	positive
21	F	6.0	6	40.5 cm (10^{th})	CT	NL	NL	Positive
22	M	6.5	7	unknown	MRI	NL	NL	positive
23	F	13.3	19	47 cm (75^{th})	MRI	NL	NL	positive

CT – head CT; VE – ventricular enlargement; EACSF – extra-axial CSF; NL – normal; (+) – above normal/increased; N/A – not applicable.

[a]Patients 4 and 7 received 40 mg/kg of rhGAA every other week.

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[b] Patient 11 died during the study; an autopsy was subsequently performed.

[c] Patient 14 died prior to the start of ERT; thus, only baseline neuroimaging is available.

[d] Patient 15 was the lone patient with non-classic IPD in this study

[*] All children had motor developmental delay

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Table 2

Summary of baseline (1st) and follow-up neuroimaging findings (n = 8) in classic infantile onset Pompe disease

Pt. No.	Sex	Age at 1st ERT (mo)	Study	Age at study (mo)	Modality	HC (percentile)	VE	EACSF	White Matter
1	M	4.7	Baseline	4.5	CT	41_cm (10th)	(+)	(+)	
			2nd study	16	CT	46.2 cm (25th)	NL	NL	
			3rd study	38	MRI	51 cm (50th)	NL	NL	NL
			4th study	158	MRI	Unknown	NL	NL	**WMH**[c]
2	M	3.1	Baseline	3	CT	38.5 cm (10th)	NL	(+)	
			2nd study	15	CT	46 cm (25th)	NL	NL	
			3rd study	64	MRI	50.7 cm (50th)	NL	NL	NL
3	F	5.4	Baseline	5	CT	42.3 cm (50th-75th)	(+)	(+)	
			2nd study	12	MRI	45.1 cm (50th-75th)	NL	NL	NL
			3rd study	24	MRI	50.9 cm (90th)	NL	NL	NL
			4th study	138	MRI	unknown	NL	NL	**WMH**[d]
4[a]	M	7.4	Baseline	7	CT	43.1 cm (25th)	(+)	(+)	
			2nd study	15	MRI	46 cm (25th)	(+)	NL	NL
			3rd study	37	MRI	48 cm (15th)	NL	NL	NL
			4th study	120	MRI	Unknown	NL	NL	NL
5	M	2.9	Baseline	9	MRI	44.5 cm (25th)	(+)	(+)	**DL**
			2nd study	50	MRI	51 cm (50th)	NL	NL	**DL** (mild)
6[b]	F	3.7	Baseline	3	CT	39.5 cm (50th)	(+)	(+)	
			2nd study	9	MRI	44.5 cm (75th)	(+	(+)	NL
7[a]	M	7	Baseline	6.5	CT	43.5 cm (50th)	(+)	(+)	
			2nd study	13	MRI	48 cm (90th)	NL	NL	NL
8	M	2.4	Baseline	2	CT	39.5 cm (50th)	NL	NL	
			2nd study	71	MRI	N/D	NL	NL	NL

CT – head CT; VE – ventricular enlargement; EACSF – extra-axial CSF; DM–delayed myelination; HC – head circumference; NL – Normal; (+) – above normal/increased; WMH – white matter hyperintensities; DL – delayed myelination; N/D – no data.

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[a] Patient 4 and 7 received 40 mg/kg of rhGAA every other week.

[b] Patient 6 was the lone CRIM-negative patient with follow-up neuroimaging.

[c] Patient 1 had diffuse abnormal periventricular white matter with subtle high signal in the basal ganglia.

[d] Patient 3 had minimal frontoparietal white matter signal change present on her last follow-up study. A prior MRA at 9 years of age was not reviewed as part of this study, but did demonstrate a basilar artery aneurysm.

[*] Myelination status cannot be assessed via CT imaging

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Table 3

Summary of key findings from the literature review.

Author (Year)	Study Desig n[a]	Modality	Baseline Study Age (Months)	Follow-up Study Age (Months)	Patients with Abnormal Study	VE	EACSF	White Matter Changes	Other CNS Abnormality
Lee *et al.* (1996)	Case report (n = 1)	MRI	5	No follow-up	1/1 (100%)	No	No	No	Dural thickening
Sahin *et al.* (1999)	Case report (n = 1)	HCT	8	Not reported	1/1 (100%)	No	No	No	Hydrocephalus
van den Hout *et al.* (2003)	Case series (n = 8)	U/S, HCT, MRI	Not reported	Not reported	2/8 (25%)	Yes (in 1)	Yes (in 1)	No	Parenchym al atrophy in 1
Chien *et al.* (2006)	Case series (n = 5)	MRI	5.5 – 8	12 – 42	5/5 (100%)	Yes (in 3)	No	Hypomyelination in all 5 at baseline with interval progression; development of deep white matter signal hyperintensities in 1	No
Burrow *et al.* (2010)	Case report (n = 1)	MRI	24	No follow-up	1/1 (100%)	Yes	No	Hypomyelination	No
Rohrbach *et al.* (2010)	Case report (n = 1)[b]	MRI	18	30, 44	1/1 (100%)	No	No	Symmetric deep white matter signal hyperintensities with interval worsening that spare the U-fibers	No
Messing er *et al.* (2012)	Case series (n = 3)[b,d]	MRI	5 – 31	54	1/3 (33%)	No	No	Development of extensive deep white matter signal hyperintensities in 1	No
Ebbink *et al.* (2012)	Case series (n = 5)	U/S, HCT, MRI	6 – 108	No follow-up	4/5 (80%)	No	No	Deep white matter hyperintensities in 4 (mean age 6 years)	No
Chien *et al.* (2015)	Case series (n = 9)[c]	MRI	7 – 18	36 – 72	7/9 (78%)	No	No	“Occasional” hypomyelination at baseline; follow-up hypomyelination in 2 and deep white matter signal hyperintensities in 5	No
Ebbink *et al.* (2016)	Case report (n = 1)[c]	MRI	108	No follow-up	1/1 (100%)	No	No	Severe symmetric white matter hyperintensities extending into the subcortical white matter with sparing of the U-fibers	No
Broomfield et al. (2017)	Case report (n=1)	MRI	48	54	1/1 (100%)	Not reported	Not reported	Predominantly frontoparietal white matter	No

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Author (Year)	Study Desig n[a]	Modality	Baseline Study Age (Months)	Follow-up Study Age (Months)	Patients with Abnormal Study	VE	EACSF	White Matter Changes	Other CNS Abnormality
								involvement at baseline; follow-up progression to include mild new bilateral involvement of external capsules	

U/S – ultrasound; MRI – magnetic resonance imaging; HCT – head computed tomography; n – # of patients; VE – ventricular enlargement; EACSF – extra-axial cerebrospinal fluid accumulation.

[a] – most studies did not report CRIM status

[b] – studies that reported CRIM negative patients

[c] – studies that reported CRIM positive patients

[d] – only 1 of the 3 patients had documented follow-up imaging