

# Classic infantile Pompe patients approaching adulthood: a cohort study on consequences for the brain

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## PUBLICATION DATA

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## ABBREVIATIONS

ERT	Enzyme replacement therapy
NEPSY-II	A Developmental Neuropsychological Assessment, Second Edition
WISC-III-NL	Wechsler Intelligence Scales for Children, Third Edition (Dutch version)

**AIM** To examine the long-term consequences of glycogen storage in the central nervous system (CNS) for classic infantile Pompe disease using enzyme replacement therapy.

**METHOD** Using neuropsychological tests and brain magnetic resonance imaging (MRI), we prospectively assessed a cohort of 11 classic infantile Pompe patients aged up to 17 years.

**RESULTS** From approximately age 2 years onwards, brain MRI showed involvement of the periventricular white matter and centrum semiovale. After 8 years of age, additional white-matter abnormalities occurred in the corpus callosum, internal and external capsule, and subcortical areas. From 11 years of age, white-matter abnormalities were also found in the brainstem. Although there seemed to be a characteristic pattern of involvement over time, there were considerable variations between patients, reflected by variations in neuropsychological development. Cognitive development ranged from stable and normal to declines that lead to intellectual disabilities.

**INTERPRETATION** As treatment enables patients with classic infantile Pompe disease to reach adulthood, white-matter abnormalities are becoming increasingly evident, affecting the neuropsychological development. Therefore, we advise follow-up programs are expanded to capture CNS involvement in larger, international patient cohorts, to incorporate our findings in the counselling of parents before the start of treatment, and to include the brain as an additional target in the development of next-generation therapeutic strategies for classic infantile Pompe disease.

Classic infantile Pompe disease is a progressive inheritable myopathy caused by a deficiency of the lysosomal enzyme alpha-glucosidase. This leads to an accumulation of glycogen that mainly affects skeletal muscles and the heart. As patients have severe mutations in the *GAA* gene, enzyme activity is less than 1% in cultured fibroblasts. Characteristically, they present before the age of 6 months with a hypertrophic cardiomyopathy, progressive generalized muscle weakness, and respiratory problems. Untreated infants die before the age of 1 year.<sup>1</sup> In 1999, the first patients with classic infantile Pompe disease were treated with recombinant human alpha-glucosidase. In 2006 enzyme replacement therapy (ERT) was registered.<sup>2</sup> Over the years, ERT has been demonstrated to significantly improve survival, cardiac, and motor outcome.<sup>2–5</sup> The first surviving infants treated in our centre are now on the threshold of adulthood.

A limitation of ERT is that it cannot pass the blood-brain barrier. However, small amounts of glycogen are also stored in the brain.<sup>6–12</sup> Therefore, we looked at the potential consequences of glycogen storage in the central nervous system (CNS) using neuropsychological tests and brain magnetic resonance imaging (MRI) from the start of therapy. Previously we found that intelligence ranged from normal to mildly delayed. Early development was easily underestimated if motor functioning was poor.<sup>5,13–15</sup> Brain MRIs showed predominantly periventricular white-matter abnormalities.<sup>15</sup> This was confirmed by a limited number of other studies on relatively young patients.<sup>16–18</sup>

As no studies have related long-term neuropsychological follow-up results to the brain abnormalities in patients up to adulthood, we had two objectives: (1) to use brain MRI and neuropsychological tests to study the long-term consequences of glycogen storage on the CNS, and (2) to relate

imaging results to our findings on neuropsychological functioning in the oldest surviving patients.

## METHOD

### Patients

ERT with recombinant human alpha-glucosidase started in 1999 with a small group of patients. For the current follow-up study, we included the 11 oldest classic infantile patients of our current cohort (start of ERT between 1999 and 2009). Four initially received recombinant human alpha-glucosidase from rabbit milk. Since 2003, all patients were treated with ERT derived from Chinese hamster ovary cells. The dose ranged from 20mg/kg every other week to 40mg/kg/week. Inclusion criteria were: *GAA* activity of less than 1%; severe mutations in the *GAA* gene; start of symptoms before 6 months; and hypertrophic cardiomyopathy at diagnosis.

Study protocols were approved by the Institutional Review Board. Written informed consent was obtained from the children's parents.

### MRI

We performed MRI of the brain at least once per patient using a 1.5T system, or a 3T system (EchoSpeed; GE Healthcare, Milwaukee, WI, USA), and a dedicated 8-channel head coil. MRIs were scanned according to a standardized protocol including T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images. MRIs were scored by assessing white matter changes in several anatomical regions, including (1) the supratentorial region: frontal and occipital periventricular white matter, the centrum semiovale, corpus callosum, external capsule, posterior and anterior limb of the internal capsule; (2) subcortical white matter, and U-fibres, and (3) the infratentorial region: decussation and cortical spinal tract at the brain-stem level. We also assessed ventricle size (lateral ventricles and fourth ventricles), and abnormal signal intensity and/or volume loss of the nucleus dentatus, basal nuclei, and thalami. All MRIs were rated by two independent evaluators: a paediatric neuroradiologist (MHL), and a paediatric neurologist (JMPvdH). If opinions diverged, consensus was reached after deliberation.

### Neuropsychological functioning

As early developmental tests in classic infantile Pompe patients can be highly influenced by motor functioning,<sup>13,15</sup> we focused on the neuropsychological test in patients over the age of 5 years. Patients underwent regular neuropsychological assessments. These were intended to assess the following: (1) age 5 years: early development; Griffiths Mental Developmental Scales (2) from 6 years onwards: intelligence; the most recent Dutch version of the Wechsler Intelligence Scales for Children, Third Edition (WISC-III-NL). The WISC-III-NL is divided into two scales or into three factors. The scales are verbal intelligence and performance intelligence. The factors are verbal comprehension, performance organization, and

### What this paper adds

- In our long-term survivors treated intravenously with enzyme replacement therapy, we found slowly progressive symmetric white-matter abnormalities.
- Cognitive development varied from stable and normal to declines towards intellectual disabilities.

processing speed. For tetraplegic children, we used the Raven Progressive Matrices.

In a subgroup of patients we tested memory (Rey Auditory-Verbal Learning Test, Memory for Designs [A Developmental Neuropsychological Assessment, Second Edition {NEPSY-II}]); language (Boston Naming Test, Comprehension of Instructions [NEPSY-II]); attention (Dot Cancellation Test, Inhibition [NEPSY-II]); executive functioning (Verbal Fluency [NEPSY-II], Digit Span [WISC-III-NL]); visual spatial functioning (Geometric Puzzles [NEPSY-II], Design Copying [NEPSY-II], Rey Complex Figure Test); processing speed (Processing Speed Index [WISC-III-NL]); behaviour (Child Behavior Checklist). All tests were administered in their most recent normed and validated Dutch versions at time of assessment. The children were assessed by two paediatric neuropsychologists (FA, BE). Two patients were tested outside our hospital, once each. One patient had an meticilline-resistant Staphylococcus aureus infection and therefore was tested in a home setting using the most recent Dutch version of the Wechsler Nonverbal Scales. The other patient was tested outside our hospital because of the initiation of her therapy in Germany. She was tested there with the most recent Dutch version of the Snijders Oomen non-verbal intelligence test-revised 2½-7. As these two time-points were important to determine development over time, we decided to include these in the data set.

Patients' test results were compared with the normative data for the Dutch population. The mean score for the intelligence tests is 100, with a standard deviation (SD) of 15 points. An IQ above 85 indicates normal development, a score between 84 and 70 indicates mild developmental delay, and a score below 70 indicates intellectual disability. A disharmonic intelligence profile was defined according to the appropriate table of the instruction manual (using the 95% confidence interval). A significant decline in IQ was defined as a loss of more than 30 IQ points (>2 SD) or a decline in raw scores, and a declining tendency as a loss of more than 15 IQ points (>1 SD).<sup>19</sup> For purposes of comparison, all neuropsychological tests were converted into z-scores. A neuropsychological test score of more than 1.5 SD below a child's total IQ represents a weaker domain.<sup>19</sup>

## RESULTS

### Patients

Table I summarizes the patient characteristics. The current age of the patients ranged from 7 years 7 months to 17 years 8 months. Motor outcome varied. Six of the 11 patients achieved the ability to walk, two of whom were still able to do so at the last evaluation. Three patients had minimal motor functioning and were respirator dependent.

**Table I:** Patient characteristics

Patient	Age at start of ERT (y:mo)	Current age (y:mo)	Invasive ventilation (age at onset, y:mo)	Mutations	CRIM status	Last LVMI Z-score<2	Hearing aids <sup>a</sup>	Impaired vision <sup>a</sup>	Best motor milestone	Last motor function
1	0:4	17:5	–	c.2481+102_2646+31del538 c.1799G>A	P	Yes	Yes	Yes	Walking	Walking
2	0:7 <sup>b</sup>	17:8	0:7	c.1115A>T c.525delT	P	Yes	Yes	Yes	MMF	MMF
3	0:2	4:4 <sup>c</sup>	2:1	c.525delT c.525delT	N	No	Yes	No	Sitting	Sitting
4	0:8 <sup>b</sup>	17:8	0:11	c.1913G>T c.1548G>A	P	No	Yes	Yes	MMF	MMF
5	0:2	4:5 <sup>c</sup>	2:0	c.2741delinsCAG c.2741delinsCAG	N	Yes	Yes	No	Walking	Sitting
6	0:1	11:10	–	c.del525T c.1933G>T	P	Yes	Yes	Yes	Walking	Sitting
7	16d	11:4	–	c.2481+102_2646+31del538 c.2481+102_2646+31del538	P	Yes	Yes	Yes	Walking	Walking
8	3d	9:0	2:8	c.1460T>C c.1460T>C	P	Yes	No	Yes	Walking	Sitting
9	0:2	8:7	–	c.525delT c.2481+102_2646+31del538	P	Yes	Yes	Yes	Standing	Sitting
10	0:2	7:7	–	c.2481+102_2646+31del538 c.2481+102_2646+31del538	P	Yes	Yes	Yes	Walking	Sitting
11	0:2	15:7 <sup>c</sup>	3:2	U	U	Yes	Yes	Yes	Sitting	MMF

All ages are stated in years and months (see also Ebbink et al.).<sup>15</sup> <sup>a</sup>Hearing and vision were sufficiently compensated at time of neuropsychological testing. <sup>b</sup>Patients 2 and 4 started therapy in the end stage of the disease; both had minimal motor function, and became ventilator dependent before the age of 1 year. <sup>c</sup>Deceased. ERT, enzyme replacement therapy; CRIM, cross-reactive immunological material; LVMI, left ventricle mass index; P, positive; N, negative; MMF, minimal motor function; U, unknown.

Three patients died at the respective ages of 4 years 4 months, 4 years 5 months, and 15 years 7 months.

### Brain MRI

In total, 21 brain MRIs were performed in 11 patients. The patients' ages at the time of MRI ranged from 7 months to 17 years 1 month. Five patients (age range 7mo–8y 6mo) had one MRI. Six patients (age range 2y 8mo–17y 1mo) had two to four MRIs. The interval between the first and last MRI was 1 year 8 months to 8 years 9 months. Table II presents the scores of all brain MRIs. At all ages, all patients had white-matter abnormalities in the centrum semiovale. Hyperintensities in the frontal and occipital periventricular areas started to appear at the age of 2 years 8 months. A tigroid hyperintensity-pattern developed in the occipital region at various ages.

After the age of 8 years 10 months (11 MRIs, five patients), MRIs started to show additional white-matter abnormalities in the subcortical areas, with sparing of the U-fibres (all patients and all MRIs), and with involvement of the external capsule (5/5 patients, 10/11 MRIs), of the posterior limb of the internal capsule (4/5 patients, 8/11 MRIs), and of the corpus callosum (4/5 patients, 9/11 MRIs). In the corpus callosum, hyperintensities were first observed in the splenium, and later in the genu and truncus. Abnormalities in the basal ganglia were found in three out of these five patients.

From the age of 11 years 4 months onwards (four patients, six MRIs), hyperintensities were noticed in the decussation (4/4 patients, 6/6 MRIs) and the corticospinal

tracts (4/4 patients, 5/6 MRIs). In addition, all patients had widening of the lateral ventricles (4/4 patients, 6/6 MRIs). The fourth ventricle was widened in only two patients (2/4 patients, 3/6 MRIs). To illustrate the progressive nature of brain involvement in classical infantile Pompe disease, Figure 1 shows the sequential MRIs of the two patients with the longest follow-up.

### Intelligence

Table SI (online supporting information) presents the total IQ scores and the scores on subscales of all patients from the age of 5 years onwards. A total of 34 intelligence tests were performed in nine patients. The age at the latest assessment ranged from 6 years to 16 years 2 months. The total intelligence scores over the period ranged from less than 45 to 121.

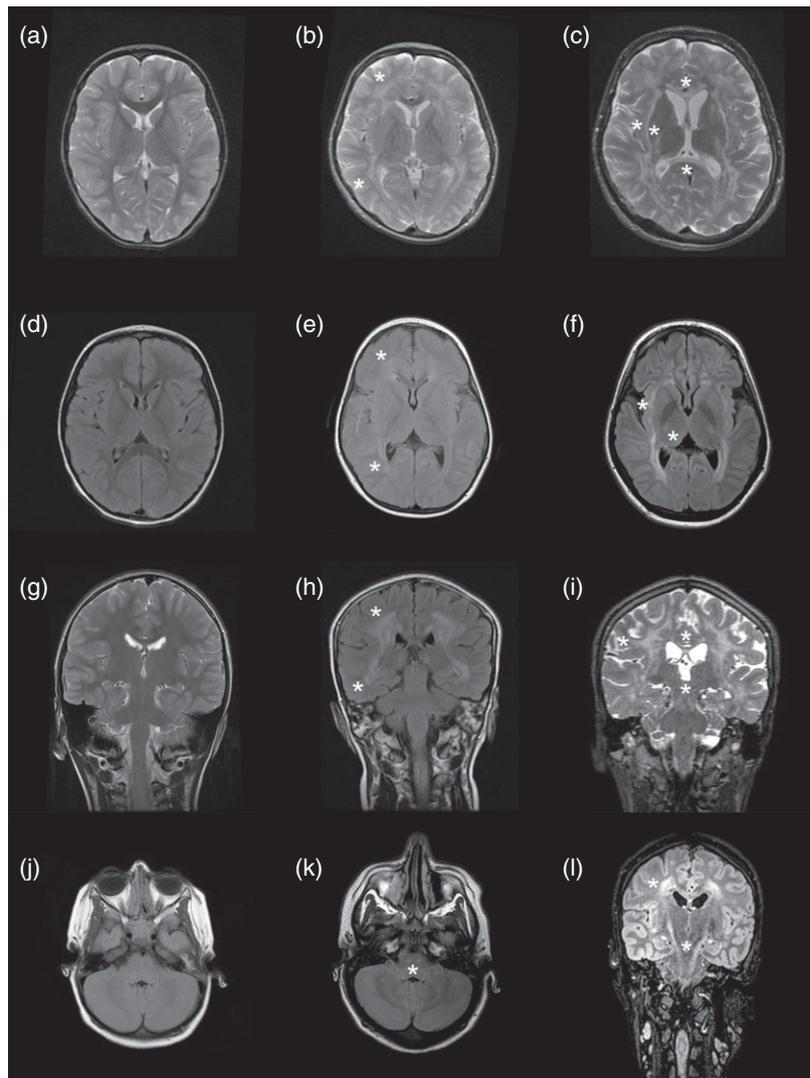
Because of the various ages and varying degrees of motor disability, it was not possible to test all patients with the same instrument. Two tetraplegic patients were tested with the Raven Progressive Matrices (patient 2 at ages 5y, 10y, and 13y; patient 4 at ages 12y and 14y). During follow-up, development was stable in both; one had normal intelligence and the other had mild developmental delay. Two other patients (patients 8 and 11) were tested with the Snijders Oomen Nonverbal Intelligence Test – Revised and the Wechsler Nonverbal Scale of Ability (age 6y and 7y). Their total intelligence scores lay in the range of intellectual disability.

Five patients (patients 1, 6, 7, 9, and 10) underwent multiple testing with the WISC-III-NL between the age of 5 years and 16 years. Figure 2 shows the total IQ, total

**Table II:** Results of the standardized scoring of magnetic resonance imaging abnormalities in patients with classic infantile Pompe disease

Patient	Age (y:mo)	PWM centrum semiovale	PWM frontal/occipital		Corpus callosum	PLIC	ALIC	External capsule	Subcortical	U-fibres	Decussation	Corticospinal	Widened lateral ventricles	Widened 4th ventricle	Basal ganglia
			frontal	occipital											
2	0:7	1	0	0	0	0	0	0	0	0	0	0	0	0	0
5	1:6	1	0	0	0	0	0	0	0	0	0	0	0	0	0
10	2:8	1	1	0	0	0	0	0	0	0	0	0	1 <sup>a</sup>	0	0
3	4:4	1	1	1	0	0	0	0	0	0	0	0	1	0	0
4	5:1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
10	5:6	1	1	0	0	0	0	0	0	0	0	0	1 <sup>a</sup>	0	0
4	5:10	1	1	0	0	0	0	0	0	0	0	0	0	0	0
10	7:4	1	1	0	0	0	0	0	0	0	0	0	1 <sup>a</sup>	0	0
9	7:6	1	1	0	0	0	0	0	0	0	0	0	0	0	0
8	8:6	1	1	0	0	0	0	0	0	0	0	0	0	0	0
4	8:10	1	1	0	0	0	1	1	0	0	0	0	0	0	0
7	9:1	1	1	1	1	0	1	1	0	0	0	1	0	0	0
6	9:6	1	1	1	1	0	1	1	0	0	1	0	0	0	1
1	9:10	1	1	1	1	0	0	1	0	0	0	0	0	0	0
7	11:1	1	1	1	1	1	0	1	0	0	0	0	0	0	0
6	11:4	1	1	1	1	1	0	1	0	1	1	1	0	0	1
11	13:8	1	1	1	1	1	0	1	1	1	1	1	1	1	1
4	13:10	1	1	0	0	0	0	1	0	1	1	1	1	0	0
11	15:4	1	1	1	1	1	0	1	1	1	1	1	1	1	1
1	15:6	1	1	1	1	1	0	1	1	1	1	0	1	0	1
1	17:1	1	1	1	1	1	0	1	1	1	1	1	1	1	1

The shades of grey reflect the severity of involvement: from light (restricted) to dark (widespread). 0=normal, '1'=slightly abnormal, 1=abnormal. <sup>a</sup>Left ventricle. PWM, periventricular white matter; PLIC, posterior limb of internal capsule; ALIC, anterior limb of internal capsule.



**Figure 1:** Long-term magnetic resonance imaging follow-up in patients with classic infantile Pompe disease. (a) Axial T2-weighted image of a healthy control patient aged 6 years. (b) Axial T2-weighted image of patient 1, aged 9 years. The asterisk indicates periventricular white-matter abnormalities. (c) Axial T2-weighted image of patient 1, aged 17 years. The asterisk indicates additional involvement of the capsula externa, posterior limb of internal capsule (PLIC), and corpus callosum. Note that the ventricles are also mildly widened. (d) Axial FLAIR (fluid-attenuated inversion recovery)-weighted image of a healthy control patient, aged 6 years. (e) Axial FLAIR-weighted image of patient 4, aged 5 years. The asterisk indicates periventricular white-matter abnormalities. (f) Axial FLAIR-weighted image of patient 4, aged 13 years. Asterisk shows the spread of white-matter abnormalities towards the capsula externa. The PLIC is slightly involved as well. (g) Coronal T2-weighted image of a healthy control patient aged 9 years. (h) Coronal FLAIR-weighted image of patient 1, aged 9 years, showing involvement of the periventricular white matter. (i) Coronal reformatted T2-weighted image of patient 1, aged 17 years. Asterisk indicates spread towards the subcortical areas and corticospinal tracts. (j, k, l) Two transversal images and one coronal FLAIR-weighted image of patient 4 at the ages of 5 years (j) and 13 years (k, l). Image (k) and (l) show involvement of the corticospinal tracts, which is not seen on image (j).

verbal IQ, total performance IQ, and processing-speed index over time. The total IQ, total verbal IQ, and total performance IQ of the two youngest patients remained stable over time (patient 9 and 10); one patient had normal development and the other had mild delay. The three patients with the longest follow-up declined in their IQ-scores. Patient 1 had a declining tendency in total IQ and total verbal IQ from normal to mildly delayed. Patient

6 had a significant decline in total IQ and a declining tendency on total verbal IQ and total performance IQ from mildly delayed to intellectual disability. Patient 7 had a declining tendency on total IQ and total performance IQ from mildly delayed to intellectual disability. All five patients declined significantly in their processing-speed index. Patients 1, 7, and 10 had disharmonic profiles at the age of 6 years (total verbal IQ > total performance IQ).

Patient 1 became harmonious after a decline in total verbal IQ, and patients 7 and 10 remained disharmonic.

### Follow-up MRI and IQ (patients 1, 6, 7, 9, 10)

To study the relationship between MRI and IQ, the IQs of the patients assessed with the Griffiths and WISC-III-NL were related to brain MRIs performed at similar ages (time between MRI and IQ assessment <1y, range 0.5–9mo). In patients with involvement of the centrum semiovale and periventricular white matter only, intelligence was normal to mildly delayed (patients' ages 2y 8mo–7y 6mo). In those with additional white-matter abnormalities, the total IQ scores indicated problems ranging from mild developmental delay to intellectual disabilities (ages of patients 9–17y). In these patients, a slight increase in white-matter involvement co-occurred with a declining tendency in their total IQ and total performance IQ (patient 7), total verbal IQ (patient 6), and processing-speed index (patients 1, 6, and 7).

### Additional neuropsychological domains

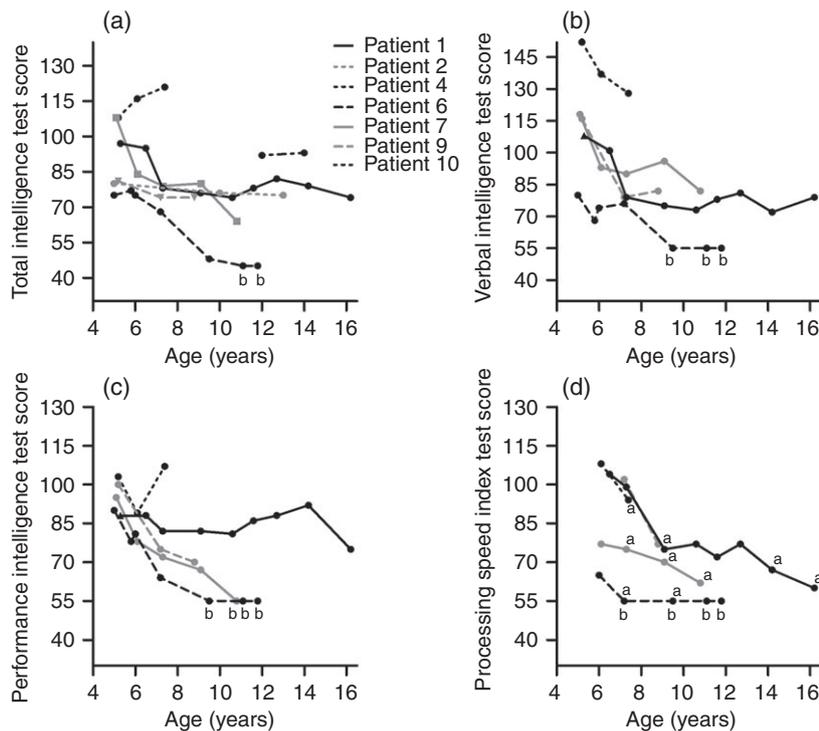
Additional neuropsychological evaluations were performed in seven patients above the age of 5 years. Attention and visual-spatial integration were tested in the five patients who were able to perform the WISC-III-NL (patients 1, 6, 7, 9, and 10). All five patients had problems in their sustained attention, but not in their selective attention.

Visual-spatial integration problems were found in three patients (3/5).

Working memory, memory, language, and executive functioning were tested in six patients. These tasks, most of which were verbal, could also be performed in one fully tetraplegic patient. Working memory was abnormal in five patients (5/6). Two patients had memory problems (2/6). No specific problems were found with regard to language (0/6) or executive functioning (0/6). The Child Behavior Checklist was administered to the parents of three patients. Social problems were found in two patients. At the ages of 12 years (patient 1) and 5 years (patient 6) there were no signs of behavioural problems on the Child Behavior Checklist. At the ages of 16 years and 7 years, 4 years and 2 years later, mild affective and mild oppositional behaviour was reported in patient 1 and mild symptoms that could be suggestive of attention-deficit-hyperactivity disorder were reported for patient 6. Mild social problems were found in both patients.

### DISCUSSION

With over 17 years of experience with ERT in patients with classic infantile Pompe disease, insights in long-term outcome are gradually expanding. As a result of ERT, survival and motor performance have improved significantly, and cardiac hypertrophy has resolved in most patients. One of the limitations of ERT is that it cannot cross the



**Figure 2:** Intelligence-test scores of patients with classic infantile Pompe disease between the ages of 5 years and 16 years. ▲=Snijders Oomen nonverbal intelligence test-revised 2½-7; ■=Griffiths Mental Developmental Scales; ●=Wechsler Intelligence Scales for Children, Third Edition (Dutch version). <sup>a</sup>Decline in raw scores in processing-speed index; <sup>b</sup>Floor effect.

blood-brain barrier. As time passes, our maturing patient population shows that the disease is not only a muscle disease, but also affects the brain.

### Brain

We noted a characteristic three-stage pattern of white-matter involvement that evolves from periventricular to subcortical and from superior to inferior. For explicatory reasons, we subdivided the process, which is likely to be gradual, into three stages. In stage one (starting around 2y of age), all the patients we evaluated had periventricular white-matter involvement at the level of the centrum semiovale. In stage two (from 8y of age onwards) the white-matter abnormalities expanded to the subcortical areas and internal and external capsule. In stage three (from 11y of age onwards), infratentorial white-matter areas also became involved.

Although there seemed to be a characteristic pattern of involvement over time, the extent of the abnormalities, and the rate of progression from stages one to three varied between patients. For example, brain MRIs in five patients aged between 8 years 6 months and 9 years 10 months showed that some had more abnormalities than others at the same age. Brain involvement appeared to be independent of motor functioning. For example, one patient who learned to walk within the normal age limits showed more abnormalities on the MRI than a patient who became tetraplegic before the age of 1 year. Although white matter changes were seen in the capsula interna, we did not note spasticity as reported by Broomfield et al.<sup>20</sup>

On the basis of all of these findings we conclude that the white-matter abnormalities on MRI in classic infantile Pompe patients indicate a varied but slowly progressive pattern of white-matter involvement.

This finding is new. To date, predominantly periventricular white-matter abnormalities that were described are consistent with our stage one.<sup>15–17,21</sup> The lack of description of progression towards more extensive white-matter involvement in earlier reports is explained by the absence of reports on MRI in children after the age of 9 years, which is when we observed progression towards stages two and three.

Nonetheless, we note variations in the rate at which the white-matter affliction progresses. These explain the three cases reported (one by our own group) that indicate more extensive white-matter disease at a relatively young age (similar to stage two).<sup>22–24</sup> Additionally, we found white-matter abnormalities in the frontal regions on brain MRIs. Theoretically this could lead to behavioural problems; this is an important aspect for future studies to consider.

### Neuropsychological profile

The variations in brain involvement are reflected by the wide range of intelligence-test scores (i.e. from normal intelligence to intellectual disabilities). This range is now wider than in earlier studies. The development over time varies from stable to neuropsychological decline. These

findings contrast with those of our previous study and of four other studies on intelligence in classic infantile Pompe disease, where cognitive development was stable, ranging from normal to mildly delayed.<sup>13,15,16,25</sup> Only one case report on a 4-year-old patient and a recent case report on a 9-year-old expressed concerns about 'a not yet fully described CNS phenotype'.<sup>23</sup>

Prompted by the potential effect of the disease on intellectual performance shown by MRI, we performed additional neuropsychological tests, whose results showed a consistent neuropsychological profile. Because of visuospatial problems, patients appeared to be at risk of a disharmonic intelligence profile. All patients also had a lower processing speed and problems in their sustained attention, and several had problems with their working memory and social interaction.

The question remains whether neuropsychological outcome can theoretically be related to the white-matter involvement we found in our Pompe patients. Firstly, the white-matter abnormalities in our patients included the frontal and parietal areas. A recent conceptual model related intelligence to the interaction between the prefrontal and parietal cortex, which relies greatly on its white-matter connectivity.<sup>26</sup> This fronto-parietal integration network is believed to be involved not only in intelligence but also in other neuropsychological functions, such as attention, working memory, and processing speed.<sup>19</sup> As the white-matter abnormalities in our patients develop within this network, it is conceivable that intelligence and these specific neuropsychological functions are affected in our patients.

A limitation of our study is that the group of patients was relatively small, although it can be considered to be large for a rare disease like classic infantile Pompe disease. A strength of the study is that we included long-term follow-up data from the four patients who were some of the first to start ERT in 1999 (of whom three are still alive) and from seven others that started ERT before 2009.

### CONCLUSION

As our patient population with classic infantile Pompe disease matures into adulthood, knowledge of this initially fatal muscle disease is broadening. It seems the brain is now becoming the next puzzle in the treatment. We advise expansion of follow-up programs to capture CNS/brain involvement in larger, international patient cohorts, inclusion of the current knowledge in the counselling of parents before the start of treatment, and inclusion of the brain as an additional target in the development of next-generation therapeutic strategies for classic infantile Pompe disease.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Table S1:** Subtest scores of intelligence tests in patients with classic infantile Pompe disease.

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**RESUMEN****PACIENTES CON LA ENFERMEDAD DE POMPE INFANTIL CLÁSICO APROXIMÁNDOSE A LA ADULTEZ: UN ESTUDIO DE COHORTE ACERCA DE LAS CONSECUENCIAS PARA EL CEREBRO**

**OBJETIVO** Examinar las consecuencias a largo plazo del depósito de glucógeno en el sistema nervioso central (SNC) por la enfermedad de Pompe infantil clásico usando terapia de reemplazo enzimático.

**MÉTODO** Usando test neuropsicológicos y resonancia nuclear magnética (RMN) de cerebro, nosotros valoramos prospectivamente una cohorte de 11 pacientes con Pompe infantil clásico de hasta 17 años de edad.

**RESULTADOS** Desde aproximadamente los dos años de edad en adelante, la RMN de cerebro mostró compromiso de la sustancia blanca periventricular y centro semioval. Después de los 8 años de edad, se agregaron anomalías en la sustancia blanca a nivel del cuerpo caloso, cápsula interna y externa y áreas subcorticales. Desde los 11 años de edad se encontraron anomalías de la sustancia blanca en tronco cerebral. A pesar de que parece haber un patrón característico de compromiso en el tiempo, hubo considerables variaciones entre pacientes reflejadas por variaciones en el desarrollo neuropsicológico. El desarrollo cognitivo varió desde estable y normal hasta declinaciones que condujeron a la discapacidad intelectual.

**INTERPRETACION** Así como el tratamiento posibilita a los pacientes con la enfermedad de Pompe infantil clásico alcanzar la adultez, las anomalías de la sustancia blanca se tornan progresivamente evidentes, afectando el desarrollo neuropsicológico. Por lo tanto, aconsejamos que los programas de seguimiento sean extendidos para evidenciar compromiso del SNC en cohortes de pacientes más numerosas e internacionales, para incorporar nuestros hallazgos al asesoramiento de los padres antes de comenzar el tratamiento, y para incluir al cerebro como un objetivo adicional en el desarrollo de nuevas generaciones de próximas estrategias terapéuticas para la enfermedad de Pompe infantil clásico.

**RESUMO****PACIENTES COM A DOENÇA DE POMPE INFANTIL CLÁSSICA CONFORME SE APROXIMAM DA VIDA ADULTA: UM ESTUDO DE COORTE SOBRE AS CONSEQUÊNCIAS PARA O CÉREBRO**

**OBJETIVO** Examinar as consequências de longo prazo do armazenamento de glicogênio no sistema nervosa central (SNC) para a doença de Pompe infantil clássica usando terapia de reposição enzimática.

**MÉTODO** Usando testes neuropsicológicos e imagens por ressonância magnética (IRM), avaliamos prospectivamente uma coorte de 11 pacientes com Pompe infantil clássica com até 17 anos de idade.

**RESULTADOS** De aproximadamente 2 anos de idade em diante, a IRM do cérebro mostrou envolvimento da substância branca periventricular e do centrum semioval. Após os 8 anos de idade, anomalias adicionais da substância branca ocorreram no corpo caloso, cápsula interna e externa, e áreas subcorticais. A partir dos 11 anos, anomalias da substância branca também foram encontradas no tronco cerebral. Embora pareça ser um padrão característico de envolvimento com o passar do tempo, houve variações consideráveis entre pacientes, refletidas por variações no desenvolvimento neuropsicológico. O desenvolvimento cognitivo variou de estável e normal para declínios levando a incapacidade intelectual.

**INTERPRETAÇÃO** Conforme o tratamento permite que pacientes com doença de Pompe infantil clássica atinjam a vida adulta, anomalias da substância branca se tornam crescentemente evidentes, afetando o desenvolvimento neuropsicológico. Portanto, aconselhamos que programas de acompanhamento sejam expandidos para captar o envolvimento do SNC em coortes de pacientes maiores e internacionais, para incorporar nossos achados no aconselhamento dos pais antes do início do tratamento, e para incluir o cérebro como um alvo adicional do desenvolvimento da próxima geração de estratégias terapêuticas para a doença de Pompe infantil clássica.