# Diagnosis and Care of Infants and Children with Pompe Disease

## Diagnostik und Therapie des Morbus Pompe im Kindesalter

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**ABSTRACT**

Pompe disease is a rare metabolic myopathy caused by deficiency of lysosomal α-glucosidase. Reduced enzyme activity results in abnormal intra- and extralysosomal glycogen deposition as well as impaired cellular function and autophagy. Age at manifestation and severity of disease depend on residual enzyme activity. Enzyme replacement therapy (ERT) is available since 2006. In infantile onset Pompe disease, the most severe form, markedly prolonged survival has resulted in a new phenotype with symptoms and problems not encountered previously. In addition, it became apparent that antibody formation against the recombinant human enzyme may adversely affect the response to ERT. This review summarizes new knowledge gained in the last years concerning care of pediatric patients with Pompe disease and gives recommendations for diagnostics, treatment, and follow-up.

**ZUSAMMENFASSUNG**

Morbus Pompe ist eine seltene metabolische Myopathie, bei der ein Mangel an lysosomaler Alpha-Glukosidase zur pathologischen intra- und extralysosomalen Speicherung von Glykogen sowie zu gestörter Autophagie führt. Je nach Alter bei Beginn können klassisch infantile sowie kindliche, juvenile und adulte Formen unterschieden werden. Alter bei Manifestation und Schweregrad hängen von der Enzym-Restaktivität ab. Seit 2006 ist eine Enzymersatztherapie (EET) verfügbar. Das verlängerte Überleben von Patienten mit infantiler Verlaufsform führt zum Auftreten neuer Symptome, die bisher bei diesen Kindern nicht beschrieben wurden. Zudem hat sich gezeigt, dass eine Antikörperbildung gegen das rekombinante humane Enzym den Erfolg der EET negativ beeinflussen kann. Dieser Artikel fasst neue Erkenntnisse zusammen, die in den letzten Jahren hinsichtlich neuer klinischer Symptome und therapeutischer Probleme gewonnen wurden, und gibt Empfehlungen für Initialdiagnostik, Behandlung und Verlaufserfassung des Morbus Pompe im Kindesalter.

## Introduction

Pompe disease is caused by biallelic mutations of the acid α-glucosidase (GAA) gene located on chromosome 17q25, that result in reduced activity of the lysosomal enzyme GAA [18]. GAA deficiency causes intra- and extralysosomal accumulation of glycogen as well as impaired autophagy [18]. Age at manifestation and rate of progression depend on residual enzyme activity. Pompe disease can be divided into an infantile onset (IOPD) and a late onset (LOPD) type [18]. The latter can be differentiated into adult, juvenile and childhood onset forms [18]. The incidence of all types amounts to approximately 1:40 000; while IOPD alone affects about 1 in 140 000 newborns [18]. LOPD manifests as a pure progressive limb girdle weakness often with early involvement of the diaphragm, whereas IOPD is a multisystemic disease affecting several other tissues including the heart [18, 44]. Infants present with creatinine kinase (CK) elevation, hypertrophic cardiomyopathy (HCM), failure to thrive, muscular hypotonia and generalized muscle weakness during the first six months of life. IOPD is rapidly progressive, and the majority of untreated subjects die within the first year of life due to a combination of respiratory and cardiac failure without achieving any motor milestones such as turning, sitting, or standing [18, 44]. Survival beyond the age of 18 months is exceptional [44]. Classic IOPD needs to be distinguished from non-classic or late-infantile Pompe disease that also manifests during infancy, but has no or much less severe cardiac hypertrophy and a somewhat better prognosis [18]. The phenotype of children diagnosed with Pompe disease beyond the first year of life is highly variable and ranges from asymptomatic children with elevated CK through subjects with delayed motor development to individuals with distinct muscle weakness [18].

Enzyme replacement therapy (ERT) with recombinant human α-glucosidase (rhGAA) (alglucosidase alfa) is available for all disease types since 2006, but the effects are variable [25–27]. Prolonged survival of IOPD patients until adolescence has resulted in a new phenotype with cardiac, speech, hearing, musculoskeletal, respiratory, swallowing, and neurocognitive features not previously encountered [16, 24, 29]. It also turned out that antibody formation against rhGAA negatively affects the response to ERT, which requires specific therapeutic interventions in some subjects. Moreover, the rhGAA dosage regimens applied in IOPD have become more variable and sometimes even differ between institutions within one country. Unfortunately, no current international recommendations concerning the care of IOPD and pediatric LOPD are available, that incorporate the new knowledge gained in recent years [16].

To define standards for diagnostics and follow-up, and to harmonize treatment of IOPD and LOPD manifesting before age 18 years in German-speaking countries, a consensus meeting with experts in this field from Austria, Germany, and Switzerland was held in June 2018. The following recommendations are based on unanimous consent by the experts and expand consensus statements given in 2012 [14].

### Diagnosis

Measurement of GAA activity at acidic pH with concomitant inhibition of other glucosidases by acarbose in leukocytes is still the diagnostic gold standard [48]. Determination of enzyme activity from dried blood spots also yields reliable results and allows subsequent genetic analysis from the same sample. GAA activity can also be measured in muscle and in cultivated fibroblasts, but for the vast majority of patients a skin or muscle biopsy is no longer required for making the diagnosis [24].

Genetic analysis of the *GAA* gene should be performed in all children with reduced GAA activity, in order to confirm the diagnosis of Pompe disease and to allow concise genetic counselling of families [24].

Although it has been shown that an early start of rhGAA treatment improves outcome in IOPD, this does not guarantee a good response to ERT in individual patients [37]. Because of this and due to difficulties in delineating patients with later onset and milder course from those with IOPD, new-born screening for Pompe disease can currently not be recommended without limitations.

GAA activity in leukocytes is less than 1 % in all patients with IOPD, but two groups have to be differentiated. While some infants synthesize a non-functional form of GAA, others are unable to produce any kind of native enzyme. The former are designated as cross-reactive immunological material (CRIM)-positive, whereas the latter are labeled as CRIM negative [28]. The CRIM status can be determined in cultivated fibroblasts or from lymphocytes. Alternatively, it can be deduced from the results of genotyping, if the effect of a specific mutation is already known. Information on the severity of about 560 GAA variants can be found in the mutation database (www.pompevariantdatabase.nl) established and regularly updated by the Pompe Center Erasmus MC at Rotterdam. Determination of the CRIM-status before start of ERT in IOPD is important since the result substantially modifies the further therapeutic approach (see below).

Other examinations meaningful at start of ERT and during follow-up are discussed in the sections concerning specific organ involvement and are summarized in ▶ **Tables 1** and ▶ **2**.

### Enzyme replacement therapy (ERT)

The algluosidase alfa dosage initially recommended was 20 mg/kg every other week for all patients with Pompe disease. Since this advice is only based on one study comparing two small groups of IOPD patients, it has been concluded that there is no robust evidence which dosing schedule is most effective in IOPD [8]. Due to the suboptimal efficacy of ERT in this age group, a substantial number of IOPD patients are now treated with higher doses than indicated in the package insert [3, 6, 9, 15, 33, 47]. Since there is some evidence that a high dose of 40 mg/kg every week is more effective than a dose of 20 mg/kg every other week [47], and to ensure that these very severely affected infants receive optimal treatment, higher doses such as 20 or 40 mg/kg every week can be applied in IOPD patients presenting with profound muscle weakness and/or severe HCM. Currently, there is no evidence that treatment with higher doses than 20 mg/kg every other week is also reasonable in LOPD.

According to the package insert, the duration of infusion is approximately 4 h. Shorter infusion times should be avoided because this increases the risk of allergic reactions. During infusion, regular monitoring of respiration, heart rate and blood pressure by qualified care givers trained to react adequately in case of allergic reactions must be guaranteed. Allergic reactions are most common after the 5$^{th}$ or 6$^{th}$ infusion, but can occur in isolated cases even after several months or years. In infants or children with poor vein

▶ **Table 1** Diagnostics at baseline in IOPD[a] and pediatric LOPD[b]

| **Enzyme activity determination[a,b]** |
|---|
| α-glucosidase activity measurement in lymphocytes and/or from dried blood spots |
| **Mutation analysis of the GAA gene[a,b]** |
| **Determination of CRIM status[a]** |
| skin biopsy with fibroblast cultivation and analysis |
| lymphocyte analysis |
| deduction from genetic testing |
| **Determination of α-glucosidase antibodies[a,b]** |
| **Assessment of respiratory status[a,b]** |
| Breathing pattern and rate, type of assisted ventilation (if applicable) |
| Arterialised blood gas analysis |
| polysomnography or pulse oximetry and capnography |
| lung function testing[b] |
| **Assessment of motor status[a,b]** |
| By AIMS (< 18 months) [a] |
| By PEDI Pompe (> 6 months)/QMFT (> 5 years) [a,b] |
| **Assessment of cardiac status[a]** |
| BNP or pro-BNP[a] |
| ECG[a] |
| Echocardiography with determination of IVS + LVPW thickness, LVMI + EF/SF[a] |
| **Assessment of nutritional status/gastrointestinal problems[a,b]** |
| Measurement of length and weight, type of nutritional support (if applicable) |
| **Assessment of hearing[a]** |
| BERA |

Abbreviations: AIMS = Alberta Infant Motor Scale, BERA = Brainstem Evoked Response Audiometry, BNP = Brain Natriuretic Peptide, CRIM = Cross-Reactive Immuno-stained Material", ECG = electrocardiogram, EF = Ejection Fraction, ERT = Enzyme Replacement Therapy, GAA = Acid Alpha Glucosidase, IVS = Intraventricular Septum, LVMI = Left Ventricular Mass Index, LVPW = Left Ventricular Posterior Wall, PEDI = Paediatric Evaluation of Disability Inventory, QMFT = Quick Motor Function Test, SF = Shortening Fraction.

▶ **Table 2** Follow-up diagnostics in IOPD[a] and pediatric LOPD[b]

| **Determination of GAA antibodies every 3[a]–6[a,b]months** |
|---|
| **Determination of immunoglobulins every 4 weeks (if applicable)** |
| **Determination of CD19 + lymphocytes every 3 months (if applicable)** |
| **Assessment of motor function[a,b]** |
| AIMS[a] / PEDI Pompe[a,b]/QMFT[a,b] every 3 months in the first year, every 6 months thereafter |
| **Assessment of cardiac status[a]** |
| BNP or pro-BNP every 2–4 weeks until distinct reduction of cardiac hypertrophy, every 3–6 months thereafter |
| ECG every 2–4 weeks until normalization of cardiac hypertrophy, every 3–6 months thereafter |
| Echocardiography with determination of IVS + LVPW thickness, LVMI + EF/SF every 2–4 weeks until normalization of cardiac hypertrophy, every 3–6 months thereafter |
| 24-hour Holter ECG every 12-months |
| **Assessment of respiratory status** |
| Lung function testing every 6 months in subjects ≥ 6 years with determination of FVC, Peak Cough Flow[a,b] (and MIP, SNIP, MEP, if applicable) |
| Polysomnography, pulse oximetry/capnography every 6-months |
| Assessment of type and duration of ventilation (if applicable) |
| **Oropharyngeal and gastrointestinal status** |
| Measurement of length and weight every 2 weeks[a,b] |
| Assessment of nutritional/gastrointestinal problems every 6 months[a,b], type of nutritional support (if applicable) |
| Diet and nutritional counselling every 6 months[a] |
| **Age-appropriate hearing assessment (every 12 months)[a]** |
| BERA / play audiometry/pure-tone audiometry/speech audiometry |
| **Age and handicap appropriate assessment of neurocognitive function[a]** |
| BSID II/III, Wechsler scales, Snijders Oomen Test, Wechsler Nonverbal Scale of Ability, Raven test at least once at pre-school age |

Abbreviations: AIMS = Alberta Infant Motor Scale, BERA = Brainstem Evoked Response Audiometry, BNP = Brain Natriuretic Peptide, CRIM = Cross-Reactive Immuno-stained Material", ECG = electrocardiogram, EF = Ejection Fraction, ERT = Enzyme Replacement Therapy, FVC = Forced Vital Capacity, GAA = Acid Alpha Glucosidase, IVS = Intraventricular Septum, LVMI = Left Ventricular Mass Index, LVPW = Left Ventricular Posterior Wall, MEP = Maximum Expiratory Pressure,, MIP = Maximum Inspiratory Pressure, PEDI = Paediatric Evaluation of Disability Inventory, QMFT = Quick Motor Function Test, SF = Shortening Fraction, SNIP = Sniff Nasal Pressure.

status, implantation of a central venous port is meaningful. Home infusion in children in a stable state without allergic reactions is principally feasible.

It has been shown that almost all CRIM-negative and some CRIM-positive patients develop high neutralising antibody titres under ERT [1, 28], and that ventilator-free survival in high-titre CRIM-negative and high-titre CRIM-positive individuals is as poor as in untreated subjects. To avoid formation of high antibody titres in CRIM-negative patients, a prophylactic immune tolerance induction with rituximab, methotrexate, and intravenous immunoglobulins (IVIG) was proposed [2], which has been proven to be effective, feasible, and safe [23]. This approach has been adopted with minor variations by many centres worldwide [3, 15, 33, 46], and can also be applied to CRIM-positive subjects developing high antibody titres (therapeutic immunomodulation) [2, 23] (▶ **Table 3**). Since prophylactic immune tolerance induction must begin before the first application of rhGAA, rapid CRIM-status determination is important. However, this should not delay the start of ERT. Therefore, IOPD patients with unknown CRIM-status should be treated as if they are CRIM-negative.

Antibodies against rhGAA should be regularly monitored in all IOPD patients, and the number of CD19 positive lymphocytes and immunoglobulin levels should be determined in those having received immune tolerance induction.

## Cardiac problems

In IOPD, accumulation of glycogen in cardiomyocytes and in the cardiac conduction system results in a severe HCM [34] with small ventricular lumen, outflow tract obstruction, and reduced ejection fraction. This causes tachycardia, weak sucking, failure to thrive,

▶ **Table 3** Treatment scheme for prophylactic and therapeutic immune tolerance induction with RTX, MTX + IVIG in IOPD (modified from reference 2)

| |
|---|
| RTX 375 mg/m$^2$ or 12.5 mg/kg if BSA < 0.5 m$^2$ followed by intravenous MTX 1 mg/kg weekly for 4 weeks (administer first doses of RTX + MTX the day before the first dose of alglucosidase alfa is given) |
| IVIG 400 mg/kg monthly starting at week 4 until B cell and IgG levels are normalized |
| Measure rhGAA-antibody titres every 3–6 months |
| Measure CD19 + B cells every 3 months until normalization |
| Determine immunoglobulin levels every 4 weeks |
| Consider antibiotic prophylaxis during the first 4 weeks |
| Discontinue MTX temporarily when neutrophil counts drop below $0.50 \times 10^9$ g/L |
| Control humeral immune response after routine vaccinations |
| Abbreviations: IOPD = Infantile Onset Pompe Disease, BSA = Body Surface Area, IgG = Immunoglobulin G, IVIG = intravenous immunoglobulins, MTX = Methotrexate, RTX = Rituximab. |

and profound sweating and dyspnea during mild efforts. ERT reverses cardiac hypertrophy and improves cardiac function within a few months in most patients. But in some individuals a dilative component of the cardiomyopathy develops with reduced contractility resulting in reduced exercise tolerance and chronic heart failure unmasks during follow-up [13].

Echocardiography is the method of choice to diagnose and follow-up HCM [24]. Brain Natriuretic Peptide (BNP) or pro-BNP are usually substantially elevated in the beginning and normalise quickly with start of ERT, reflecting improved cardiac function [13, 24]. Drug therapy with Angiotensin Converting Enzyme inhibitors, calcium antagonists and beta-blockers can be indicated, but these medicaments should be used with caution and only by a paediatric cardiologist experienced in treating paediatric patients with heart failure [24]. General anaesthesia should be limited to a minimum, particularly in young infants and should only be carried out by anaesthetists with experience in managing general anaesthesia in children with heart disease [24].

Apart from HCM, different cardiac arrhythmias such as nonsustained and sustained supraventricular tachycardia, atrial or ventricular premature beats, and ventricular tachycardia or fibrillation have been reported in patients with IOPD [30, 35, 43]. This demonstrates that careful and regular monitoring of cardiac function is important, even when cardiac hypertrophy has been ameliorated [43].

## Musculoskeletal problems

All patients with IOPD display some residual axial muscle weakness, ranging from mild (independent walking) through moderate (free sitting) to severe (no sitting without support) [16]. Distribution of muscle weakness differs from what is seen in older patients with LOPD, since the facial muscles, the neck flexors, the hip extensors, and the foot dorsiflexors are particularly affected [5]. After several years of treatment, even subjects responding initially well to ERT show progression of muscle weakness, often causing loss of acquired motor milestones [3, 15, 16, 33]. Older ambulant IOPD patients have a characteristic gait pattern with forward leaning of the trunk and increased lordosis due to pelvic tilt, as well as steppage gait caused by prominent weakness of the foot dorsiflexors [5, 38]. Marked lumbar hyperlordosis together with progressive scoliosis may require spinal fusion in some. The disproportional strength of foot flexors and extensors may necessitate use of ankle foot orthoses [5, 24, 29]. Like in other neuromuscular disorders IOPD patients require provision with orthopaedic devices and wheelchairs as appropriate, while immobility predisposes to osteopenia [24].

Prominent weakness of the neck flexors, rigid spine, and marked muscle wasting are symptoms observed in many patients with LOPD manifesting during childhood or adolescence [18, 29]. Monitoring and treatment in LOPD differ not principally from other neuromuscular disorders with paediatric onset.

The AIMS (Alberta Infant Motor Scale) is suitable for recording the motor status in the first 18 months of life while the more elaborate PEDI Pompe test (Paediatric Evaluation of Disability Inventory) and/or the simple QMFT (Quick Motor Function Test) can be applied thereafter [4, 24].

## Respiratory problems

Muscle weakness in Pompe disease regularly includes the respiratory muscles [32], with involvement of the diaphragm in 50 % of the patients. Inspiratory muscle strength can be evaluated by determination of maximum inspiratory pressures and sniff nasal inspiratory pressures, or simply by measurement of vital capacity (VC) [32]. A distinct decline of VC from the sitting to the supine position is indicative of diaphragm weakness [32]. Diagnosis of diaphragm weakness can be achieved clinically when paradoxical breathing appears in the supine position in combination with increase of respiratory rate and activation of auxiliary respiratory muscles. IOPD patients with reduced inspiratory muscle strength are prone to acute respiratory failure during respiratory tract infections and to chronic respiratory failure manifesting as nocturnal hypoxemia and hypoventilation [32]. Nocturnal hypoventilation occurs in 50 % of IOPD patients [22], which is comparable to the frequency of nocturnal hypoventilation associated with diaphragm weakness in LOPD [31]. Therefore, respiratory function in IOPD patients should be monitored closely by clinical examination or lung function testing, and by polysomnography or at least measurement of nocturnal $SaO_2$ and end tidal $CO_2$/transcutaneous $CO_2$ at regular intervals [24, 32]. It is widely accepted that nocturnal hypoventilation in children and adults with neuromuscular disorders needs to be treated by invasive or non-invasive ventilation [19].

Furthermore, respiratory muscle weakness frequently results in cough insufficiency that predisposes to mucus accumulation, atelectasis and pulmonary infection. Cough insufficiency can be assessed by measuring the peak cough flow [32] and is treated by application of an airway clearance technique in addition to conventional physiotherapy [7]. Mechanical insufflation-exsufflation is the most frequently used airway clearance technique for patients with neuromuscular disorders and is also recommended in children [19].

## Speech and hearing problems

In IOPD, glycogen disposition in the inner hair cells of the cochlea predisposes to sensorineural hearing loss [20, 21]. Some patients also have additional conductive or retrocochlear hearing loss. Hearing thresholds vary from 10 to 90 dB. Capelle and co-workers found

that 4 out of 11 patients had profound hearing loss (> 60 dB) at age 0–4 months, while 8 out of 10 had thresholds greater than 60 dB at age 1–6 years, which suggests that hearing loss increased with time in some and was not improved by ERT [42].

Facial and oropharyngeal muscle weakness is reflected by bilateral ptosis, an expressionless face, and a tent-shaped mouth with dropping of the lower lip. IOPD patients also have reduced tongue and lip mobility in conjunction with velopharyngeal incompetence, resulting in dysfunctional articulation, hypernasal resonance, disordered phonation and prosody, and flaccid dysarthria. Altogether, this leads to a characteristic monotone hoarse and wet voice with substantially reduced speech intelligibility [24, 42].

The high risk of progressive hearing impairment necessitates regular assessment of hearing every 12 months, and fitting with hearing aids if appropriate. Oro-facial muscle function and speech can be trained by special forms of physiotherapy and language therapy [16, 22, 42].

### Oropharyngeal and gastrointestinal problems

IOPD subjects display oral dysmotility with lip incompetence, tongue thrust, and upper oesophageal sphincter dysfunction. This predisposes to oral and pharyngeal residues, nasal regurgitation, and delayed initiation of swallow [19, 40, 45]. Swallowing difficulties often lead to nutrition with soft or liquid foods containing high amounts of sugar. Together with a long retention time in the oral cavity, this predisposes to the development of profound caries [16, 19, 24, 40, 45]. These features require monitoring of growth parameters, securing adequate caloric intake and caries prophylaxis [16, 24]. A lower total energy intake often results in reduced protein and micronutrient intake causing failure to thrive [16, 26]. Consequently, Pompe patients should be tested and supplemented for such deficiencies. It has been advised that adult Pompe patients should consume 1.2–1.4 g/kg protein per day, which is above the intake recommended for the general population (0.8–1.0 g/kg), and that a balanced multi-vitamin supplement is meaningful [41]. Whether other supplementations (e. g. creatine monohydrate) or specific diets (e. g. ketogenic diet) are beneficial has not yet been systematically analysed [41].

Dysphagia and gastro-oesophageal reflux increase the risk of pneumonia [16, 17]. Enteral nutrition via a nasogastric tube or via gastrostomy is important in patients with inadequate caloric intake, and Nissen fundoplication will minimize the risk of aspiration in those with severe gastro-oesophageal reflux [16, 17].

### Neurocognitive problems

Low amounts of glycogen are stored in the brain of patients with IOPD [34].Signal alterations predominantly of the central white matter and progressive in some individuals, have been reported by several authors [4, 11, 12, 36, 38]. Earlier reports assessing neurocognitive function in smaller groups of patients suggested a normal or only mildly delayed cognitive development [10, 39]. But a recent study, following a cohort of 11 IOPD patients up to 17 years of age by neuropsychological testing found a broad performance spectrum ranging from normal cognitive function to intellectual disabilities [12]. Although severity and frequency of intellectual problems in IOPD remain to be elucidated, these findings justify assessment of neurocognitive function in IOPD at least before entering school. Tests that can be applied depending on age of the patient include the Bayley Scales of Infant Development (BSID II/III) and the Wechsler scales (WIPPSI, WISC, WAIS). Since standardized neuropsychological testing is difficult in children with multiple handicaps, speech and hearing impairment may necessitate the use of non-verbal tests such as the Snijders Oomen Nonverbal Intelligence Test, the Wechsler Nonverbal Scale of Ability, or the Raven test [12, 14].

### Supportive care

Treatment of children with IOPD and LOPD by far exceeds mere ERT. Especially in IOPD, the multisystemic features require a close collaboration of many medical and non-medical disciplines such as metabolic specialists, child neurologists, neurologists, cardiologists, pulmonologists, ear, nose and throat specialists, gastroenterologists, anaesthetists, physiotherapists, speech therapists, social workers, and many others. Because of the complex phenotype and the sophisticated therapy children with Pompe disease should be in charge of or supervised by an institution specialised in treating such patients.

## Conclusions

Pediatric Pompe disease has become a treatable disease within the last 10–15 years. ERT has transformed IOPD from a rapidly progressive disease lethal in the first year of life into a chronic condition with a still high mortality and morbidity. Since current treatment strategies are far from being perfect further huge efforts are necessary to improve the outcome of affected children. Second generation recombinant enzymes with higher levels of mannose-6-phosphate residues with or without concomitant chaperone therapy are currently in clinical trials [16]. Gene therapy using vectors targeting not only skeletal and cardiac muscles, are further promising research topics [16].

## Conflict of Interest

The authors declare that they have no conflict of interest.

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