Reuser was 4.2 years (range 0.3–12.0). Two of the eleven patients proved to respond to enzyme-replacement therapy (ERT) with recombinant human alpha-glucosidase. Of the remaining 9 patients, 2 showed a conductive hearing loss, 7 patients had a sensorineural hearing deficit (5 pts with a cochlear dysfunction and 2 pts with a retro-cochlear pathology) and just one had a mixed pattern. Our observations revealed that, in this group of late onset Pompe patients, the auditory impairment is often present (60% of Pompe patients). Our data emphasize the importance of monitoring the auditory function since childhood in all patients with Pompe disease.

P3.55
CRIM status and antibody formation in patients with classic infantile Pompe disease treated with enzyme-replacement therapy

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Pompe disease is an autosomal recessive disorder caused by deficiency of lysosomal acid alpha-glucosidase (GAA). Total deficiency of this enzyme in severely affected infants leads to massive glycogen storage in all tissues and affects the heart, lungs, and brain. The survival of affected infants depends on the implementation of enzyme-replacement therapy (ERT) with recombinant human alpha-glucosidase. Remaining patients develop high antibody titers against the recombinant enzyme. However, similarly high antibody titers have also been reported in affected adults with Pompe disease. We determined the CRIM status of 11 patients receiving ERT, both in CRIM-negative patients and CRIM-positive patients.

P3.56
Analysis of the screening process for Pompe disease at the Cuiabá University Teaching Hospital, Brazil in 2010

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Pompe disease, also known as glycogen storage disease type II, is an autosomal-recessive metabolic disorder of varying degrees of penetration. In patients with late onset form, skeletal and respiratory muscle weakness is progressive and differential diagnosis must be made with muscular dystrophy. This study aims to identify patients with Pompe disease among patients with progressive muscle weakness attending the neurolology clinic at Cuiabá University Teaching Hospital. This observational, cross-sectional clinical study consists of descriptive analysis of 48 patients receiving care at neurolology, pediatric neurology and genetic clinics in Cuiabá during 2010. Patients were referred by pediatric and clinical medicine departments of this hospital or by the state healthcare appointment scheduling system. For enzyme activity tests, dried blood spot (DBS) sample on filter paper was obtained from all patients with progressive muscle weakness, history of frequent falls or whose physical examination revealed reduction, albeit mild, in muscle strength. Forty-eight patients, 64.5% of whom were male, were evaluated. Mean age of patients was 16.6 years (range 2 days to 59 years). Screening identified one patient with Pompe disease (2%) and 10 (20.8%) who had DBS borderline result and fibroblasts culture remain developing. Diagnosis was confirmed by fibroblast culture and gene mutation testing. The rest of the sample, dried blood spot testing was negative. Of these patients, 7 were diagnosed with progressive muscular dystrophy. Results of electromyographies and muscle biopsies of the remaining 26 patients who tested negative for Pompe disease are yet to be received. Studies show that implementation of enzyme replacement therapy alters the prognosis of disease, enabling stabilization of patient’s clinical condition and even reversal of lesions caused by intracellular accumulation of glycogen.

P3.57
Clinical features, disease progression and prognostic factors of muscle weakness in adults with Pompe disease

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Adults with Pompe disease, a metabolic myopathy caused by acid alpha-glucosidase deficiency, usually suffer from slowly progressive limb-girdle weakness and respiratory problems. The disease has a considerable phenotypic variability. Prospectively gathered data on the natural disease course are important for timing the start of enzyme replacement therapy and for evaluating its efficacy. This prospective cohort study in 94 adults describes the clinical variability, the rate of disease progression, and defines prognostic factors for disease progression. Muscle strength (by manual muscle
testing and hand held dynamometry) and pulmonary function (forced vital capacity in sitting and supine position) were measured in a standardized way every 3–6 months. The mean age of the patients was 50 years (range 25–75 years). Muscle weakness was most pronounced in the limbgirdle and proximal muscles of the lower extremities and in the trunk muscles. A substantial number of patients had less well-known features such as ptosis (23%), flaccid dysarthria and dysphagia (28%), or scapular winging (33%). During follow-up (average 1.6 years, range 0.5–4.2 years) muscle strength deteriorated significantly by 1.3% points/year for manual muscle testing and by 2.6% points/year for hand held dynamometry. The rate of deterioration in muscle strength correlated significantly with disease duration and pulmonary function at study entry. Forced vital capacity deteriorated by 1% per year in sitting position (p = 0.06) and by 1.3% per year in supine position (p = 0.02). The nine patients that remained stable had milder disease severity and shorter disease duration as compared to the total group. The clinical features in adults with Pompe disease vary and disease progression is usually slow. Longer disease duration and abnormal pulmonary function appeared to be prognostic factors for a more rapid decline in muscle strength.

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P3.58
Differences in clinical spectrum in families with Pompe disease
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Pompe disease is an autosomal recessive disorder caused by mutations in the GAA-gene. The clinical spectrum is broad and even in patients with the same genotype variations in phenotype are observed. The aim of this study is to describe the clinical spectrum in families. Genotype in the Netherlands 17 families with adult Pompe disease are known. Sixteen families have the most common mutation c.-32-13T>G in combination with another pathogenic mutation. One family has the c.1447G>A/c.569G>A genotype. Gender males are most severely affected in 5 families and females in 2 families. In the other families there is no difference between males and females or the siblings are all the same gender. Age in 10 families the oldest sibling and in 5 families the youngest sibling has the most severe symp- toms. In 2 families the siblings are equally severely affected. Onset of symp- toms in 9 families there is a difference in onset of symptoms between siblings of less than 10 years. In 5 families the difference is 10–20 years and in 3 families this is more than 20 years. Level of weakness in 10 families the MRC-sumscore differs less than 20 points (out of 130) between siblings at the same age or first visit. In 7 families this is more than 20 points. Disability in 11 families there is at least one sibling wheelchair dependent, while another sibling is ambulant. In 8 families there is at least one sibling ventilation dependent, while another sibling is not. In 2 fami- lies the one with the shortest disease duration is wheelchair and ventilation dependent. Pompe patients with the same GAA-genotype can have a dif- ferent phenotype, indicating that other factors influence the clinical course. This study shows that the clinical spectrum in families can largely differ between siblings. Additional studies are needed to identify factors that contribute to the clinical differences.

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P3.59
Remarkably low acid alpha-glucosidase activity in two patients with adult-onset Pompe disease
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Pompe disease in adults usually presents as a limb-girdle myopathy and is caused by pathogenic mutations in the GAA-gene. The majority of the adult patients have the c.-32-13T>G mutation in 1 GAA allele, resulting in reduced enzyme activity, and a fully deleterious mutation in the other. In the Dutch population the activity of acid alpha-glucosidase in these patients ranges from 7.3 to 19.9 nmol/mg.h. We present 2 adult patients that don’t have the common c.-32-13T>G null genotype, but novel pathogenic mutations that encode much lower enzyme activity. A 25-year-old man experienced problems with lifting objects since the age of 15 and lost his ability to run at the age of 20 due to progressive limb-girdle weakness. He had proximal weakness MRC-grade 3–4 of the upper and lower extremities. FVC was 75% (upright) and 65% (supine) of predicted. The acid alpha-glucosidase activity in fibroblasts was 1.0 nmol/mg.h and the GAA genotype was c.569G>A/c.1447G>A. Transient expression assays revealed that both mutations lead to almost complete loss of acid alpha-glucosidase activity. The second patient is a 55-year-old man with progressive limb-girdle weakness since the age of 26. He became wheelchair and ventilation dependent at the age of 45. The acid alpha-glucosidase activity in fibroblasts was 0.5 nmol/mg.h and his GAA genotype was c.671G>A/c.525delIT. Also in this case, transient expression assays revealed that both mutations lead to almost complete loss of acid alpha-glucosidase activity. We present two cases of Pompe patients in which the acid alpha-glucosidase activity in fibroblasts is far below the activity that is mostly measured in patients with onset of symptoms in adulthood. From these observations we conclude that the clinical course of Pompe disease can’t in all cases be predicted from the level of residual acid alpha-alglucosidase activity that is expressed in the fibroblasts.

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P3.60
Pompe disease in persons with unclassified Limb-girdle muscular dystrophy
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Pompe disease is a rare glycogen storage disease (type II), caused by deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). The late onset adult form of Pompe disease is characterised by progressive skeletal muscle weakness and wasting, and a reduced respiratory func- tion causing an increased morbidity and mortality. Enzyme replacement therapy is now available, and it is important to diagnose patients early, before skeletal muscle damage becomes irreversible. In 2008, only two