Respiratory Medicine (2009) **103**, 477–484

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Pompe disease: A neuromuscular disease with respiratory muscle involvement

Uwe Mellies [a,*], **Frédéric Lofaso** [b]

[a] *Department of Pediatric Pulmonology and Sleep Medicine, University of Essen, Children's Hospital, Essen, Germany*
[b] *Department of Physiology-Functional Testing, and Centre for Technological Innovation, Garches, and Inserm UMR 841, Créteil, France*

Received 4 August 2008; accepted 11 December 2008
Available online 7 January 2009

KEYWORDS
Acid maltase deficiency;
Glycogen storage disease type II;
Pompe disease;
Respiratory complications;
Type II glycogenosis

Summary
Pompe disease is a single disease continuum that includes variable neuromuscular symptoms and rates of progression. However, specific clinical features, such as an early onset of respiratory problems preceding limb muscular weakness, distinguish Pompe disease from other neuromuscular diseases in which respiratory insufficiency occurs after loss of ambulation. The management of Pompe disease also differs from other neuromuscular diseases in that specific treatment is now available, making early recognition of the disease a priority. The results from clinical trials with recombinant human acid α-glucosidase have been published, and they show promising results with regards to the improvement of respiratory function in patients with Pompe disease.

This review aims to give an overview of Pompe disease and to describe the current concepts of the disease. A focus is placed on the pathophysiology and clinical presentation of respiratory muscle involvement in adults. Additionally, new approaches and therapies available for the management of respiratory complications observed in Pompe disease are discussed in detail.

Contents

* Corresponding author. Department of Pediatric Pulmonology and Sleep Medicine, University of Essen, Children's Hospital, Hufelandstrasse 55, D-45122 Essen, Germany. Tel.: +49 201 723 2231; fax: +49 201 723 2352.
E-mail address: uwe.mellies@uni-due.de (U. Mellies).

0954-6111/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2008.12.009

Introduction

Pompe disease

Pompe disease, also termed glycogen storage disease type II or acid maltase deficiency, is a serious and often fatal condition of glycogen metabolism.[1] The disease is an autosomal recessive disorder, which manifests clinically as a progressive neuromuscular disease and presents varying rates of progression.[1] Pompe disease is a single disease continuum occurring at any age with remarkable phenotypic variation, as well as variable rates of progression and extent of organ involvement.[1,2] The prevalence of Pompe disease is estimated to vary between 1 in 40,000 and 1 in 600,000, depending on geographical and ethnic factors.[3,4]

Originally described by, and named after, Dr J. C. Pompe in 1932, the disease is characterized by the lysosomal accumulation of glycogen in numerous tissues of affected individuals.[1] Massive glycogen deposits occur as a result of defects in the activity of the glycogen degrading lysosomal enzyme, acid α-glucosidase (GAA).[1] Clinical presentation and disease severity are primarily determined by the amount of residual GAA enzyme activity, with the most severely affected patients having no detectable enzyme activity.[5] No strict relationship exists between genotype and phenotype;[2] only a few mutations have been described which are common in specific ethnic groups.[1,2] Additionally, metabolic factors can also be involved, as a few patients have been identified with a mild phenotype, but little functional GAA in their lysosomes.[5]

In symptomatic patients, the diagnosis of Pompe disease is based on low GAA activity in skin fibroblasts or blood samples.[5] Additionally, muscle biopsy, although more invasive, can be used for the determination of GAA activity or for histological studies. However, the site of biopsy can influence results due to variability in glycogen content between muscles.[5] A genetic profile confirms the diagnosis of Pompe disease.[5]

Respiratory involvement

Respiratory involvement in Pompe disease differs from other inherited neuromuscular diseases, especially Duchenne muscular dystrophy.[6] In contrast to other neuromuscular diseases, where respiratory insufficiency occurs after loss of ambulation, respiratory symptoms in Pompe disease can be one of the first clinical manifestations of the disease, and patients may present respiratory impairment despite still ambulating.[6] A recent case study described a patient with Pompe disease that walked into a clinic carrying his artificial respirator.[7] Similar to other neuromuscular diseases, reduced vital capacity and weakness of the expiratory muscles result in reduced cough and ineffective clearance of airway secretions leading to recurrent chest infections.[5,8] Diaphragm weakness with sleep disordered breathing and respiratory failure also seem to be an inevitable part of the Pompe disease course.[5,6,9,10] Respiratory failure in patients with Pompe disease can range from insidious to acute onset.[8,11–13] Cases cited in the literature have reported symptoms of fatal obstructive sleep apnea,[11] and hypoventilation.[11,14] Respiratory muscle involvement is the most common cause of early death in patient's with Pompe disease, as well as in other patients with primary neuromuscular disease.[9]

Objective of this review

Due to the low prevalence and wide range of symptoms, Pompe disease is often unrecognized by physicians, and the majority of patients eventually die from complications of respiratory muscle weakness. Therefore, as treatment with enzyme replacement is now available, this review is intended to enhance recognition of Pompe disease by pulmonologists and other physicians.

This review will discuss the pathophysiology and clinical presentation of respiratory muscle involvement seen with Pompe disease, and will inform physicians involved in the treatment of these patients about the new approaches and therapies that are available for the management of respiratory complications.

Methodology

A MEDLINE search was carried out using the key-terms 'Pompe disease', 'acid maltase deficiency', 'glycogen

storage disease', 'respiratory', and 'pulmonary'. The literature search was performed without time constraints in order to ensure that all existing literature on the pulmonary aspects of Pompe disease was found.

Results

Clinical symptoms and respiratory aspects of Pompe disease

In general, muscle weakness in Pompe disease is symmetrical but imbalanced across joints, with greater weakness in proximal muscles rather than distal, and lower extremities rather than upper.[1] Muscles can look hypertrophic and feel firm to the touch despite profound weakness.[1] Furthermore, respiratory muscles and the diaphragm are affected; hence respiratory dysfunction that affects sleep, daily life activities, and quality of life is common in the course of neuromuscular disorders.[15]

The clinical symptoms of Pompe disease show a significant variability with respect to age of onset, extent of organ involvement, and rate of progression.[1,15] A retrospective chart review by Kishnani et al.[16] reported that in infants, the median age of symptom onset was 2 months, the median age at diagnosis was 4.7 months, and the median age at death was 8.7 months. In older children and adults, Pompe disease has a wider range of age of onset, and a slower rate of progression.[17,18] In adults, the first symptoms start at a mean age of 28 years[17,19] and were mostly related to mobility problems and limb-girdle weakness.[17] The delay in diagnosing Pompe disease is generally too long; more than 5 years for over half of the adults studied.[17,19] On average, adult patients with Pompe disease start mechanical ventilation at the age of 50 years,[15,17] which is 10 years later than the average age of diagnosis. Combined with the finding that many patients start mechanical ventilation during an episode of acute respiratory failure,[15] at diagnosis, patients should be referred to a pulmonologist for regular evaluation and timely initiation of respiratory aids when necessary, to avoid potentially catastrophic situations during acute chest colds.

Symptoms in infants

Prominent features of infantile Pompe disease are cardiac muscle involvement and heart failure.[20] All affected infants have general muscle weakness, the so-called 'floppy baby syndrome', and they certainly always have some respiratory muscle involvement.[1,16–18,20] Any situation that requires an increase of alveolar ventilation/respiration, such as fever and/or a simple upper airway infection, is therefore unmasking the underlying insufficiency.[1,21] Marsden[22] reported that disease progression was characterized by increased respiratory distress in 72% of cases examined. Additionally, respiratory failure was a common sign noted on physical examination.[22]

In summary infantile Pompe disease is the most severe subtype, and without treatment, the disease course is rapidly progressive and fatal, with death due to cardiac failure occurring before the age of 2 years.[1]

Symptoms in patients with childhood- and adulthood-disease onset

The primary symptom of Pompe disease in about one third of adult cases is respiratory failure (or symptoms that indicate respiratory insufficiency, such as dyspnea on exertion, reduced physical capacity, recurrent pulmonary infections, etc.).[1,12,13,19,22,23] However, the onset of respiratory involvement in adults may be very subtle, and a thorough review of the literature reveals that respiratory symptoms were preceded by slight limb muscular weakness (e.g. inability to run, un-athletic appearance, etc.).[1,24]

In two-thirds of patients, respiratory symptoms increase with Pompe disease progression and include a progressive loss of respiratory muscle function, decrease of vital capacity, sleep disordered breathing, impaired cough, chronic respiratory insufficiency, and finally cor pulmonale, and acute respiratory failure.[6,11,14,15,18,25]

In contrast to Pompe disease in infants, disease progression in older children and adults is generally slower, and although the skeletal muscles are predominantly affected, ambulation is often preserved for years.[1,11] The respiratory muscles involved are the upper airways, inspiratory muscles of the chest, and the diaphragm.[5] In some patients with Pompe disease, involvement of the upper airways might lead to obstructive sleep apnea that might be independent from the involvement of the other respiratory muscles.[8] However, predominat involvement of the diaphragm and its progressive weakness is the characteristic feature in these patients.

Depending on the severity of the diaphragmatic weakness and the reduction of the vital capacity respiration is compromised in a typical pattern. At first, respiration is only compromised during sleep, presenting as nocturnal hypoventilation during REM-sleep which is mostly pronounced due to physiologic atonia of chest wall muscles and dependency of respiration on the diaphragm. Patients are presenting with symptoms of unrestful sleep, nocturnal awakening with dyspnea, nightmares and morning headaches due to hypercarbia, etc.[5,8] When Pompe disease progresses, patients develop hypoventilation during the day (CO_2 >45 mmHg), and in the end stages, also hypoxemia (PO_2 <60 mmHg), cor pulmonale and death.[5,8] During this chronic course, the situation might exacerbate at any time due to a respiratory infection, fever, injury, or surgery.[5,8] In addition, patients with Pompe disease present with acute or chronic respiratory failure because of their inability to adequately increase respiration.[5,8] In the latter stages of the disease, reduced vital capacity and weakness of the expiratory muscles result in reduced cough and ineffective clearance of airway secretions, leading to recurrent chest infections.[5,8]

Respiratory evaluation of patients with Pompe disease

Although there is a weak relationship between respiratory and locomotor functions in adults with Pompe disease, respiratory function should be monitored independently from the degree of peripheral muscle weakness.[15] The respiratory status of patients with Pompe disease should

be evaluated at each physician or hospital visit, since deterioration can occur continuously or in a stepwise manner.[6,8] Attention should especially focus on the ability of the patient to cough, shortness of breath, exercise tolerance, energy level, and degree of fatigue-ability.[5] In addition, a patient's history should include the frequency and severity of lower airway infections, sleep quality, snoring, observed apneas, and morning headaches.

Respiratory function testing should differentiate inspiratory and expiratory weakness and/or upper airway muscle involvement.[6] Based on the shape of the normal pressure-volume curve, one would expect a considerable loss of respiratory muscle strength before observing a fall in vital capacity (VC) and other lung volumes.[26] Actually, the relationship between VC and maximal pressures generated by the inspiratory muscle is more linear than curvilinear in the Pompe disease population.[15] Therefore, a decrease in VC is an early sign of respiratory impairment, and routine evaluation to assess pulmonary function should include VC measurement with spirometry.[6] It is very helpful to study the change in VC that occurs when patients with Pompe disease switch from the upright to the supine position, which gives a simple index of diaphragm weakness relative to the other inspiratory muscles.[27] – which is a characteristic feature in Pompe disease.[6] Thus, a normal supine VC excludes clinically relevant inspiratory muscle weakness.[28] Periodic assessment of VC is important because thresholds of VC have been shown to predict treatment complications and outcomes in patients with neuromuscular disease.[6] Some physicians consider maximum insufflation capacity as a better prognostic factor than VC in neuromuscular patients.[29–31] Sniff inspiratory nasal pressure and maximum inspiratory mouth pressure are both complementary techniques that are non-invasive volitional maneuvres. These techniques give a measurement of inspiratory muscle strength; predicted normal values adjusted for age and sex are available for both adults and children.[26,32]

Transdiaphragmatic pressure measurement requires esophageal pressure and gastric pressure measurements, but it has the advantage of directly quantifying diaphragmatic weakness.[15,26,28] This quantification can be established by asking the patient to do volitional maneuvres and, when these maneuvres are equivocal, by stimulating the phrenic nerve.[15,26,28] Effective cough, and the different methods that might assist it, can be appreciated by the ability to generate expiratory airflow during peak flow or cough maneuvres.[33–35] Effective cough is considered adequate when peak cough flow it is >200 L/min in both adults[36] and children,[34,35] although a recent study indicated that values <255 L/min could predict the risk of an ineffective spontaneous cough during a respiratory tract infection.[37]

Gas exchange and acid-base status should be also be evaluated to assess the functional consequence of respiratory muscle weakness[26] and the development of respiratory failure. However, factors other than muscle weakness can contribute to hypercapnia, such as abnormalities of the chest wall that increase the elastic load imposed on the inspiratory muscles of neuromuscular patients,[38] and which can be partially reversed with mechanical ventilation in Pompe disease.[39] Elevation of bicarbonate concentration (>4 mmol/L) can provide an important clue on the occurrence of nocturnal hypercapnia.[26,40] Chest radiographs can prove useful for diagnosis of clinical deterioration or of hypoxemia incompletely explained by alveolar hypoventilation.[5] Basal atelectasis is frequently observed[12] and is explained by the disproportionate weakness of the diaphragm. In addition, all patients suspected of Pompe disease should give a detailed history of their sleeping patterns at diagnosis and during follow-up appointments.[5,6]

Sleep studies (polysomnography [PSG]) should be undertaken regularly in order to detect sleep disordered breathing. Pompe disease patients with a VC of <60% of predicted when in the supine position might have sleep disordered breathing (typical desaturations during REM sleep).[6] A VC of <40% is a strong predictor for continuous nocturnal hypoventilation, and a VC of <25%, for respiratory failure.[5,6] Therefore, in advanced disease, screening with overnight pulse-oxymetry could be sufficient to detect nocturnal hypoventilation.[5] Although PSG is the gold standard, it is not generally available, but should be performed when symptoms are suggestive and when the VC (supine) is <60% of predicted.[5]

Respiratory interventions/treatments

Treatment of respiratory symptoms or respiratory support might be necessary because the prognosis of untreated chronic respiratory failure is poor in patients with Pompe disease.[11] Two techniques designed to assist breathing during failure of the respiratory muscles have been described in the literature: non-invasive positive pressure ventilation (NIPPV); and assisted coughing.[8] NIPPV has emerged as the standard therapy for acute and chronic respiratory failure despite the lack of prospective randomized trials.[8] NIPPV can be used for managing most patients with Pompe disease, including those with extremely low or unmeasurable VC.[8] However, some patients cannot be managed by NIPPV, and tracheotomy is then required.[8] Although the impact of long-term NIPPV on survival has been demonstrated, there is much debate regarding the appropriate time for the introduction of either intermittent or continuous NIPPV, i.e. instituted for permanent respiratory failure versus nocturnal hypoventilation.[11] Patients with nocturnal hypoventilation and sleep apnea syndrome are likely to benefit from the timely introduction of NIPPV by having significantly improved sleep and a reduction in daytime symptoms, such as morning headaches, lack of appetite, sleepiness, and impaired concentration.[8]

To remove respiratory secretions in patients with ineffective cough capacity, several groups have evaluated cough augmentation methods based on mechanical hyperinflation techniques,[29–31,33,34,41] and/or manual and/or mechanical expiratory assisted coughing.[31,33] These techniques, and especially the mechanical insufflator–exsufflator, might be of benefit in order to assist clearance of airway secretions, avoiding tracheostomy for secretion clearance or ventilatory failure in patients with Pompe disease with insufficient cough due to neuromuscular disease.[8] In patients with Pompe disease, inspiratory muscle weakness is more pronounced than expiratory weakness and, therefore, assisted coughing will not reduce the need of NIPPV in these patients.

Chest infections are the main cause of respiratory failure in patients with neuromuscular disease with pre-existing respiratory compromise.[8] Therefore, the prevention of chest infections should be a major goal of treatment, and the clearance of mucus secretions from airways and maintenance of sufficient cough are measures that can be used to reduce the frequency of chest infections and hospital admissions.[35] Proactive monitoring and treatment programs, including regular assessments of lung function and early antibiotic treatment, are likely to improve outcome and quality of life for many patients with Pompe disease.[8]

Management issues during anesthesia

The progressive infiltration of glycogen in the heart and skeletal muscle results in a severe form of cardiomyopathy and respiratory muscle weakness.[42] As a result, the anesthetist faces significant problems in the management of patients with Pompe disease.[42] Pre-operatively, the question of whether the benefit of surgery justifies the anesthetic risk must be raised. A thorough pre-operative examination should include the detection of associated cardiac and respiratory dysfunction.[43] Anesthetic experience in Pompe disease is limited because of the short life expectancy.[42,44,45] McFarlane and Soni[42] described a patient who had a cardiac arrest after induction with inhaled halothane and subsequently underwent a safe anesthesia with ketamine. Kotani et al.[44] reported their experience with a general anesthetic administered to an 11-year-old boy with severe Pompe disease. The patient received enflurane and N_2O to eliminate the need for intra-operative administration of muscle relaxants or other drugs that cause respiratory depression.[44] However, the boy had post-operative respiratory failure and required ventilator support.[44] The authors concluded that the administration of a volatile anesthetic and the avoidance of muscle relaxants do not protect patients with Pompe disease from post-operative respiratory failure.[44] Additionally, Kotani et al.[44] emphasized that post-operative respiratory failure should be anticipated for all patients with Pompe disease undergoing a general anesthetic, regardless of the anesthetic drugs used.

Key factors in successful anesthesia outcome are attention to anesthetic technique and close monitoring.[42] Given the high propensity toward myocardial ischemia, a five-lead electrocardiogram (ECG) with continuous ST-segment monitoring and placement of an indwelling arterial catheter should be strongly considered.[45]

Management of patients with Pompe disease

In general, adults with Pompe disease report significantly poorer quality of life than the general population on the physical functioning, general health, vitality, and social functioning scales.[46] More specifically, wheelchair use is associated with lower physical and social functioning scores, and the use of artificial ventilation with lower physical functioning scores.[46]

Physical therapy, such as gentle facilitation of movement with active, graded assistance in infants, and aerobic functional exercise with active assistance in adults might preserve motor and physiologic function in patients, as well as maximizing the benefits of enzyme replacement therapy.[47]

Net muscle protein degradation in adults affected by Pompe disease is believed to be a major contributing factor to the muscle weakness and wasting of the disease.[48] The combination of nutrition and exercise therapy, designed to decrease muscle glycogen deposit and to increase muscle fatty acid utilization, has been reported to slow the progression of Pompe disease.[48] However, the beneficial effects of nutrition and exercise therapy for adult patients with Pompe disease needs to be confirmed in a large, prospective, randomized, multicenter study, with careful monitoring of compliance by caregivers.[48]

Enzyme replacement and other emerging therapies

Enzyme replacement therapy

Recently, alglucosidase alfa (recombinant human GAA, Myozyme®; Genzyme Corporation, Cambridge, MA, USA) was approved by the European and US authorities for the treatment of Pompe disease (20 mg/kg body weight administered every 2 weeks as an intravenous infusion). Patients across the spectrum of Pompe disease (infants, juveniles, and adults) have been treated with alglucosidase alfa in clinical trials, case series, and case studies.

Clinical studies in infants have shown that early treatment with alglucosidase alfa is associated with improved response.[24,49] The safety and efficacy of alglucosidase alfa treatment has been evaluated in a clinical trial of 18 severely affected infants with Pompe disease who began treatment before 6 months of age.[49] Kishnani et al.[49] reported that treatment with alglucosidase alfa in infants resulted in a reduced risk of invasive ventilation and of any type of ventilation (92 and 88%, respectively), compared with an untreated historical control group. All 18 patients in this open-label study were alive at age 18 months (100%) compared with 1.9% (95% CI 0—5.5%) in an untreated historical control group.[49] A second trial included 21 older infants with Pompe disease aged between 6 and 36 months.[50] During the first year of therapy with alglucosidase alfa, 76% of infants with Pompe disease survived, 83% of patients showed a reversal of cardiomyopathy, and 48% acquired new motor mile stones.[50] Comparing these results with the 100% survival in infants treated before 6 months of age suggests better outcomes with early treatment.

In both infants and adults, it has also been shown that the response of muscle and respiratory functions to alglucosidase alfa therapy seems to be related to the condition of the affected patient at baseline.[24,51] A study by Van den Hout et al.[52] reported the respiratory course of four patients with Pompe disease before and after alglucosidase alfa treatment. The four patients in this study responded differently to the treatment, although the age of the patient at the start of treatment and symptoms at inclusion seemed to play a role in outcome.[52] The two younger patients (aged 2.5 and 3 months) showed no significant respiratory symptoms at inclusion. However, one of the

patients became ventilator dependent at the age of 2 years after a surgical procedure. The second patient had an uneventful respiratory course. The two older patients started treatment when they were aged 7 and 8 months. Both remained ventilator dependent, even though other symptoms improved during treatment with alglucosidase alfa.[52] Thus, early recognition of symptoms and a confirmed diagnosis of Pompe disease are crucial in order to achieve optimal therapeutic benefit for patients.

Alglucosidase alfa has also been studied in juveniles and adults with Pompe disease. Van der Ploeg and Marsden[51] recently presented the outcomes of 18 severely affected juvenile and adult patients with Pompe disease who were treated with alglucosidase alfa. Ten patients demonstrated improvements in respiratory function.[51] A preliminary report of a study in patients with Pompe disease by Van der Ploeg et al.[53] showed that in five patients, with a median treatment age of 12 years (range 5–15 years), improvements in respiratory function and motor function were observed after 38 infusions of alglucosidase alfa.[53] In a study of five ventilator-dependent patients with a mean ± SD age of 48 ± 14 years, at week 52 of treatment with alglucosidase alfa, two patients were able to breath without a ventilator (1 and 2 h/24 h), and two showed mild improvements in slow VC sitting and supine, maximal inspiratory and expiratory pressures, and transdiaphragmatic pressures.[54] Preliminary results from the Late Onset Treatment Study (LOTS), a multicenter, randomized, double-blind, placebo-controlled trial on the efficacy and safety of alglucosidase alfa in 90 pediatric and adult patients >8 years, showed improvements in walking and pulmonary outcomes compared with placebo. By 78 weeks, a mean absolute difference of 3.4 ± 1.2% in percentage predicted forced VC was observed in favor of alglucosidase alfa ($P = 0.003$) (baseline mean forced VC was 54.6 ± 14.8%).[55] The availability of an effective treatment emphasizes the importance of early diagnosis and early initiation of treatment in Pompe disease.

Other therapies

Other therapies in development for Pompe disease include the experimental adeno-associated virus vector-mediated gene therapy and putative chemical chaperones such as deoxynojirimycin.[56,57] Both experimental therapies hold promise for the availability of a curative therapy.[56,57] In preclinical studies, Okumiya et al.[57] demonstrated that chemical chaperones could mobilize mutant lysosomal GAA species that are trapped in the endoplasmic reticulum and Golgi compartments, and partly restore their catalytic function.

Necessity to evaluate treatment of patients with Pompe disease

Longitudinal collection of patient data, whether or not they receive specific treatment, is essential in order to increase our understanding of Pompe disease and to monitor patients, with the ultimate goal of improving the management and the clinical outcome of patients. The Pompe Disease Registry (http://www.pomperegistry.com) is a database of medical information on patients with Pompe disease. Physicians can use the collective information from the registry to broaden their knowledge of the disease, and to monitor the effectiveness of management strategies.

Conclusions

Pompe disease is a multi-system disorder; hence it is best managed by a multidisciplinary team, including a metabolic disease geneticist, a physical therapist, and other specialists according to the specific disease manifestations. Considering the frequent, and sometimes early, respiratory involvement in Pompe disease, a pulmonologist with a good knowledge of neuromuscular disease should be included in the team. Regular pulmonary function tests and sleep studies are mandatory.

There is a necessity to collect longitudinal patient data. National and international registries, such as the Pompe Disease Registry, can be useful for understanding and monitoring this disease and the efficacy of treatment.

The recent development of a specific treatment, in the form of enzyme replacement therapy with alglucosidase alfa, along with other classical treatments including physical therapy and non-invasive ventilation might modify the natural course of the illness. This could, therefore, lead to physicians being able to recognize and diagnose Pompe disease as early as possible, in order to maximize the clinical and functional benefits of treatment.

Acknowledgements

We thank Klara Belzar, PhD and Corine Visser, PhD for providing writing and editorial assistance.

Conflict of interest statement

The authors received writing/editorial support from Excerpta Medica in preparation of this manuscript, funded by Genzyme Europe BV. The authors are fully responsible for content and editorial decisions for this manuscript.

References

1. Hirschhorn R, Reuser AJJ. Glycogen storage disease type II: acid acid-glucosidase (acid maltase) deficiency. In: Scriver CR, Sly WS, Childs B, Beaudet AL, Valle D, Kinzler KW, Vogelstein B, editors. *The metabolic and molecular bases of inherited disease*. 8th ed. McGraw-Hill Medical; 2001. p. 3389–420.
2. Raben N, Plotz P, Byrne BJ. Acid alpha-glucosidase deficiency (glycogenosis type II, Pompe disease). *Curr Mol Med* 2002;**2**: 145–66.
3. Ausems MG, Verbiest J, Hermans MP, et al. Frequency of glycogen storage disease type II in The Netherlands: implications for diagnosis and genetic counselling. *Eur J Hum Genet* 1999;**7**:713–6.
4. Pinto R, Caseiro C, Lemos M, et al. Prevalence of lysosomal storage diseases in Portugal. *Eur J Hum Genet* 2004;**12**: 87–92.

5. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. *Genet Med* 2006;**8**:267—88.
6. Mellies U, Dohna-Schwake C. Neuromuscular disorders. In: Hammer J, Eber E, editors. *Pediatric pulmonary function testing*. Basel: Karger; 2005. p. 1—14.
7. Burghaus L, Liu W, Neuen-Jacob E, Gempel K, Haupt WF. Glycogenesis Type II (M. Pompe). Selective failure of the respiratory musculature — a rare first symptom. *Nervenartz* 2006;**77**:181—6.
8. Mellies U, Dohna-Schwake C, Voit T. Respiratory function assessment and intervention in neuromuscular disorders. *Curr Opin Neurol* 2005;**18**:543—7.
9. Howard RS, Wiles CM, Hirsch NP, Spencer GT. Respiratory involvement in primary muscle disorders: assessment and management. *Q J Med* 1993;**86**:175—89.
10. Sivak ED, Salanga VD, Wilbourn AJ, Mitsumoto H, Golish J. Adult-onset acid maltase deficiency presenting as diaphragmatic paralysis. *Ann Neurol* 1981;**9**:613—5.
11. Mellies U, Ragette R, Schwake C, Baethmann M, Voit T, Teschler H. Sleep-disordered breathing and respiratory failure in acid maltase deficiency. *Neurology* 2001;**57**:1290—5.
12. Rosenow 3rd EC, Engel AG. Acid maltase deficiency in adults presenting as respiratory failure. *Am J Med* 1978;**64**:485—91.
13. Sander HW, Menkes DL, Hood DC, Williams DA. A 60-year-old woman with weakness, fatigue, and acute respiratory failure: case report and discussion of the differential diagnosis. *Mil Med* 1998;**163**:715—8.
14. Culebras A. Diaphragmatic insufficiency in REM sleep. *Sleep Med* 2004;**5**:337—8.
15. Pellegrini N, Laforet P, Orlikowski D, et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *Eur Respir J* 2005;**26**:1024—31.
16. Kishnani PS, Hwu WL, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 2006;**148**:671—6.
17. Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain* 2005;**128**:671—7.
18. Hagemans ML, Hop WJ, Van Doorn PA, Reuser AJ. Van der Ploeg AT. Course of disability and respiratory function in untreated late-onset Pompe disease. *Neurology* 2006;**66**:581—3.
19. Müller-Felber W, Horvath R, Gempel K, et al. Late onset Pompe disease: clinical and neuorphysiological spectrum of 38 patients including long-term follow-up in 18 patients. *Neuromuscul Disord* 2007;**17**:698—706.
20. Van den Hout HM, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* 2003; **112**:332—40.
21. Akcam M. Infantile Pompe's disease presenting with pulmonary infections during the newborn period. *Saudi Medical J* 2004; **25**:2022—3.
22. Marsden D. Infantile onset Pompe disease: a report of physician narratives from an epidemiologic study. *Genet Med* 2005;**7**: 147—50.
23. Keunen RW, Lambregts PC, Op de Coul AA, Joosten EM. Respiratory failure as initial symptom of acid maltase deficiency. *J Neurol Neurosurg Psychiatry* 1984;**47**:549—52.
24. van der Ploeg AT. Monitoring of pulmonary function in Pompe disease: a muscle disease with new therapeutic perspectives. *Eur Respir J* 2005;**26**:984—5.
25. Escolar DM, Wokke JH, Pestronk A, Carter GT, Jaffe KM, Laforêt P. Clinical presentation and disease progression in late-onset Pompe disease. *Neuromuscular Disord* 2006;**16**:654 [Abstract G.P.1 01].
26. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;**166**:518—24.
27. Fromageot C, Lofaso F, Annane D, et al. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. *Arch Phys Med Rehabil* 2001;**82**:123—8.
28. Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995;**50**:1131—5.
29. Kang SW, Bach JR. Maximum insufflation capacity. *Chest* 2000; **118**:61—5.
30. Kang SW, Bach JR. Maximum insufflation capacity: vital capacity and cough flows in neuromuscular disease. *Am J Phys Med Rehabil* 2000;**79**:222—7.
31. Sivasothy P, Brown L, Smith IE, Shneerson JM. Effect of manually assisted cough and mechanical insufflation on cough flow of normal subjects, patients with chronic obstructive pulmonary disease (COPD), and patients with respiratory muscle weakness. *Thorax* 2001;**56**:438—44.
32. landelli L, Gorini M, Misuri G, et al. Assessing inspiratory muscle strength in patients with neurologic and neuromuscular diseases: comparative evaluation of two noninvasive techniques. *Chest* 2001;**119**:1108—13.
33. Trebbia G, Lacombe M, Fermanian C, et al. Cough determinants in patients with neuromuscular disease. *Respir Physiol Neurobiol* 2005;**146**:291—300.
34. Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U. IPPB-assisted coughing in neuromuscular disorders. *Pediatr Pulmonol* 2006;**41**:551—7.
35. Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U. Predictors of severe chest infections in pediatric neuromuscular disorders. *Neuromuscul Disord* 2006;**16**:325—8.
36. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. *Chest* 1996;**110**:1566—71.
37. Sancho J, Servera E, Díaz J, Marín J. Predictors of ineffective cough during a chest infection in patients with stable amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2007;**175**: 1266—71.
38. Misuri G, Lanini B, Gigliotti F, et al. Mechanism of CO_2 retention in patients with neuromuscular disease. *Chest* 2000;**117**:447—53.
39. Vercken JB, Raphael JC, de Lattre J, Fromageot C, Fanjoux J. Adult maltase acid deficiency myopathy: treatment with long-term home mechanical ventilation. *Biomed Pharmacother* 1988;**42**:343—9.
40. Hukins CA, Hillman DR. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. *Am J Repir Crit Care Med* 2000;**161**:166—70.
41. Simonds AK, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998;**53**:949—52.
42. McFarlane HJ, Soni N. Pompe's disease and anaesthesia. *Anaesthesia* 1986;**41**:1219—24.
43. Klingler W, Lehmann-Horn F, Jurkat-Rott K. Complications of anaesthesia in neuromuscular disorders. *Neuromuscul Disord* 2005;**15**:195—206.
44. Kotani N, Hashimoto H, Hirota K, Muraoka M, Matsuki A. Prolonged respiratory depression after anesthesia for parathyroidectomy in a patient with juvenile type of acid maltase deficiency. *J Clin Anesth* 1996;**8**:620.
45. Ing RJ, Cook DR, Bengur RA, et al. Anaesthetic management of infants with glycogen storage disease type II: a physiological approach. *Paediatr Anaesth* 2004;**14**:514—9.
46. Hagemans ML, Janssens AC, Winkel LP, et al. Late-onset Pompe disease primarily affects quality of life in physical health domains. *Neurology* 2004;**63**:1688—92.
47. Case LE, Kishnani PS. Physical therapy management of Pompe disease. *Genet Med* 2006;**8**:318—27.
48. Slonim AE, Bulone L, Goldberg T, et al. Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. *Muscle Nerve* 2007;**35**:70—7.

49. Kishnani PS, Corzo D, Nicolino M, et al. Recombinant human acid (alpha)-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007;**68**:99—109.
50. Nicolino M. Alglucosidase alfa: first available treatment for Pompe disease. *Therapy* 2007;**4**:271—7.
51. van der Ploeg AT, Marsden DL. Physician reported outcomes of enzyme replacement therapy in older, severely affected patients with Pompe disease. *Mol Genet Metabol* 2007;**90**:257.
52. Van den Hout JM, Kamphoven JH, Winkel LP, et al. Long-term intravenous treatment of pompe disease with recombinant human alpha-glucosidase from milk. *Pediatrics* 2004;**113**: e448—57.
53. van der Ploeg AT, Marsden DL. Response to treatment with Myozyme in juvenile patients with Pompe disease. *Mol Genet Metabol* 2007;**90**:257.
54. Orlikowski D, Laforet P, Pellegrini N, et al. Effects of one year enzyme replacement therapy in severe form of late onset pompe disease. Severe Late Onset Treatment Study (French SLOTS) 60th Annual Meeting of American Academy of Neurology; Apr 12—19, 2008; Chicago, IL. Abstract P02.121.
55. van der Ploeg AT, Clemens PR, Corzo D, et al. Results from a randomized, double-blind, multicenter, multinational, placebo-controlled study of the safety and efficacy of Myozyme, recombinant human acid alpha-glucosidase (rhGAA), for the treatment of pompe disease in juveniles and adults [abstract]. Presented at the 60th Annual Meeting of American Academy of Neurology; Apri 12—19, 2008; Chicago, IL. Abstract LB2.001.
56. Koeberl DD, Kishnani PS, Chen YT. Glycogen storage disease types I and II: treatment updates. *J Inherit Metab Dis* 2007;**30**: 159—64.
57. Okumiya T, Kroos MA, Vliet LV, Takeuchi H, Van der Ploeg AT, Reuser AJ. Chemical chaperones improve transport and enhance stability of mutant alpha-glucosidases in glycogen storage disease type II. *Mol Genet Metab* 2007;**90**: 49—57.