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Workshop report

208th ENMC International Workshop: Formation of a European Network to develop a European data sharing model and treatment guidelines for Pompe disease Naarden, The Netherlands, 26–28 September 2014

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1. Introduction

In September 2014, twenty-two experts in the field of Pompe disease from nine European countries gathered in Naarden, The Netherlands, for a workshop on Pompe disease. Experts were mostly physicians with clinical experience in treating and following larger groups of patients with Pompe disease and in doing research on this disease. Additionally, an epidemiologist, a basic scientist and a patient representative were present. The aim of the workshop was three-fold:

1 establish a European Network on Pompe disease;
2 agree on a minimal dataset of outcome measures for adult patients;
3 develop recommendations on start and stop criteria for ERT for adult Pompe patients.

Pompe disease, or glycogen storage disorder type II, is a rare inherited metabolic disorder caused by deficiency of the lysosomal enzyme acid alpha-glucosidase which results from mutations in the alpha-glucosidase gene of which more than 300 have been identified (www.pompecenter.nl). It presents as a spectrum of phenotypes, ranging from a rapidly fatal phenotype in infants, who usually die within the first year of life from cardiorespiratory failure, to more slowly progressive forms in older children and adults, in whom skeletal and respiratory muscles are mainly affected.

Since 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase has been approved for the treatment of Pompe disease. Studies in neonates showing improved survival were key to market approval [1–4]. Since then several studies in children and adults have shown effects of ERT on walking distance, pulmonary function, muscle strength and function and recently also on survival [5–7]. However, the results also suggest that there is a large variation in the effects of treatment in these patients.

With an incidence of approximately 1:40,000 to 1:200,000 births, research progress on this rare disease is slow, hampered by the difficulty to obtain sufficient patient numbers. For example, very little is known about which factors explain the variation in the response to treatment that is observed both in children and adults. Also, guidance on monitoring and treating these patients is relatively scarce. There are currently no internationally accepted guidelines for the treatment (ERT) of older children and adults with Pompe disease, although national guidelines have been published for several European and non-European countries [8–16]. Finally, the development of centres of expertise and European Reference Networks in the field of rare diseases shows that there is an increasing need for organizations with focussed knowledge on specific rare diseases, including Pompe disease, to provide advice and leadership.

International collaboration can facilitate these issues. Combining clinical, biological and genetic data from different European countries would generate a sufficiently large dataset to allow research into prognostic factors to progress. Furthermore, the joint experience of experts who monitor and treat relatively large numbers of patients with Pompe disease would create a platform to develop recommendations on monitoring and treating

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patients. Finally, their shared knowledge and experience makes them an ideal organization to provide advice and knowledge to health authorities and policy makers. This workshop was initiated specifically to form a European Network on Pompe disease in order to facilitate research, develop recommendations, and be an organization that health authorities can contact.

Prior to the meeting all participants received a questionnaire asking which assessments were used for adult patients and which start and stop criteria were applied in the participants' country and/or clinic. This information, as well as information from the literature, was presented at the beginning of the discussion sessions. Through group discussions with all participants consensus was reached on all three topics. Because the assessments used and start and stop criteria applied may differ between infants, children and adults, this meeting focussed on reaching consensus on these two topics for adult patients only.

This paper presents the results of the workshop with respect to the three aims. The recommendations for starting and stopping ERT in adult patients are summarized. The full recommendations with their evidence base will be harmonized in a next consortium working group meeting and published separately.

2. Formation of a European Network

This session started with a presentation highlighting the potential benefits of forming a network. The International Guillan-Barré Outcome Study network (IGOS) was used as an example to show how data can be shared successfully in an international context (www.GBSstudies.org). A further presentation listed a number of choices that have to be considered when setting up a network: what will be its focus and how will the network be organized.

All participants were in favour of forming a European network. It was agreed that the network will be composed, initially, of the experts invited to the meeting. Participation covered nine European countries: Belgium, Denmark, France, Germany, Italy, the UK, The Netherlands, Spain and Turkey. Over time, the network is likely to expand to involve more European countries, and later possibly also experts from countries outside Europe.

The organization of the network with a steering board group, one national representative for each country, and other members, was also discussed. It was agreed that the organizers of the workshop will propose a formal governance structure for the network. This will be incorporated in a final consortium agreement, outlining the structure and rules of the network. All members will be asked to sign this agreement.

Areas the network intends to focus on include data sharing and collaborating on research questions, developing recommendations on starting and stopping ERT, standards of care and harmonization of outcome measures, as well as responding to questions from health authorities.

3. Minimal dataset for adult patients

To initiate this session, the results of the questionnaire showing which different outcome measures are assessed in the different participating countries for adult patients were presented. This overview (Table 1) showed that many different outcome measures are being used, but also indicated some clear overlaps. Each country representative then briefly presented which data were collected in their country and how. Participants then discussed which outcome measures should be included in a minimal dataset to be used for data sharing purposes. This was discussed for each of the different clinical domains affected in adult patients (i.e. skeletal muscle strength and function and pulmonary function), and also patient reported outcomes and other information were considered.

Agreement was reached on a minimal dataset to be used for data sharing purposes (Fig. 1). All clinical assessments selected were commonly used in the participating countries and deemed to be relatively simple to use. The selected clinical assessments are also recommended for use in monitoring the patient's response to treatment. Further information on each of the assessments is given below.

3.1. Muscle strength

Manual muscle testing using the Medical Research Council (MRC) grading scale [17] was selected to assess muscle strength. To ensure these data are consistent, the scale ranging from 0 to five without +/− notification should be used. It was decided not to use the Rasch-built MRC at this time, despite its clinimetrical advantages, since all centres have been performing the standard MRC score for several years and it is important that follow-up data are consistent. Muscle groups to include are (left and right side if applicable): neck extensors, neck flexors, shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip extensors, hip abductors, hip adductors, knee flexors, knee extensors. Muscle groups not included were the shoulder adductors, exorotators and endorotators, since these are relatively difficult to measure and to standardize, and the strength of these muscles is usually reflected by the arm abductors. Measuring grip strength was excluded since this is only affected at a very late stage of the disease.

Hand-held dynamometry and quantitative muscle testing are means to assess the muscle strength more precisely in Newtons. These tests were not selected for the minimal dataset primarily because of problems with reproducibility and because they are currently not uniformly performed across the centres.

3.2. Muscle function

The 6-minute walk test (6MWT) and four timed tests (TT) were selected to assess muscle function. The 6MWT provides information on endurance as well as walking speed [18]. A downside is that it is not suitable for wheelchair bound patients. A major reason to include the 6MWT is that it has been used as a major clinical outcome measure in all clinical trials of adults, and as a monitoring tool in many centres, allowing for long-term follow-up and comparability with other studies.

Four other timed tests were included because they reflect aspects relevant in daily life, and because most centres are used to examine them: walking 10 metres, climbing four steps, standing up from supine position and standing up from a chair.

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Table 1
Overview of assessments used in the participating countries.

Assessments	Belgium	Germany	Denmark (Copenhagen)	France	Italy	The Netherlands	Spain (Madrid)	UK
Muscle strength								
MRC	+	+	+	+	+	+	+	+
HHD	+	+	0	0	p	+	+	+
QMT	0	0	0	p	p	+	0	0
Biodex	0	p	+	p	0	0	0	+
Functional tests								
6MWT	+	+	+	+	+	+	+	+
Timed tests	+	+	+	+	+	+	+	+
WG	0	+	0	+	p	+	+	0
B&V	+	0	0	+	p	+	0	0
MFM	+	p	0	+	p	0	0	0
0ther	0	0	0	0	0	QMFT	NSA	0
Pulmonary function								
(F)VC sitting	+	+	+	+	+	+	+	+
(F)VC supine	+	+	+	+	p	+	+	+
MIP/MEP	0	+	0	+	p	+	+	p
TDP	0	p	0	p	0	0	0	0
Sleep	+	+	+	+	p	i	i	+
Patient reported outcomes								
RHS	0	p	0	+	p	+	+	+
SF-36	0	+	0	0	p	+	+	+
FSS	0	0	+	+	p	+	+	+
Other	0	0	0	0	0	R-PACT	0	0

MRC – Manual muscle testing using the Medical Research Council grading scale; HHD – Hand-Held Dynamometry; QMT – quantitative muscle testing; 6MWT – six minute walk test, TT – timed tests; WG – Walter Gardner scale; B&V – Brook & Vignos scale; MFM – Motor Function Measure, derived from GMFM to be performed by physiotherapist; QMFT – quick motor function test; NSA – North Star Ambulatory Assessment; (F)VC – forced vital capacity; MIP/MEP – maximum inspiratory/expiratory pressure; TDP: transdiafragmatic pressure; Sleep: sleep studies; RHS: Rotterdam Handicap Scale (participation); SF-36: Short-Form 36 (quality of life); FSS: Fatigue Severity Scale; R-PACT: Rasch-built Pompe-specific Activity scale (participation).
Symbols: + – assessment used in the country (or city), 0 – not used, p – in some centres only, i – on indication.

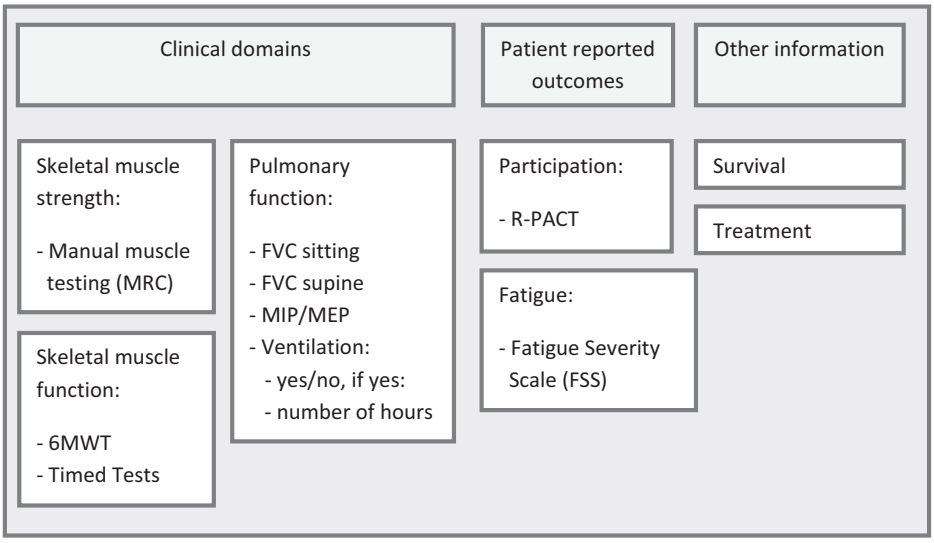

Fig. 1. Domains affected in adult Pompe patients and minimal set of outcome measures. MRC – the Medical Research Council grading scale (ranging from 0 to 5); 6MWT – six minute walk test; Timed tests: walking 10 metres, climbing four steps, standing up from supine position and standing up from a chair; MIP/MEP – maximum inspiratory/expiratory pressure, FVC – forced vital capacity; R-PACT – Rasch-built Pompe-specific activity scale, FSS – fatigue severity scale.

It is also important to record whether each of the TT could be performed or not, to distinguish missing values (or zero values) from being unable.

3.3. Pulmonary function

Forced vital capacity (FVC [19]) in sitting and supine positions, and maximal inspiratory/expiratory pressure (MIP/MEP [19]) were included to assess pulmonary function. It is important to measure FVC in both sitting and supine position because diaphragmatic weakness is common in Pompe disease. MIP/MEP were selected in addition to FVC as these provide information on respiratory muscle strength rather than capacity as measured by FVC. Finally, it is important to record whether the patient is ventilated (yes/no), and if so the

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number of hours of ventilation and whether ventilation is invasive or not.

3.4. Patient reported outcomes

Although it is important to assess quality of life (QoL), the SF-36, a commonly used generic measure of QoL, was not selected. Preference was given to a disease-specific activity scale, the new Rasch-built Pompe-specific activity scale (R-PAct). This brief questionnaire consists of 18 items and was developed to measure Pompe patients' ability to carry out daily life activities and social participation [20].

Fatigue is a commonly reported problem in Pompe patients [21]. The fatigue severity scale (FSS) is a generic nine-item questionnaire that evaluates the severity and impact of fatigue [22]. No disease-specific equivalent exists for Pompe patients. A Rasch-based version of this questionnaire has been developed, but was not selected, because the full FSS has been used in several centres over a longer period of time, and because its score can be translated into the Rash-version.

3.5. Other information

To allow the dataset to be used for analyses of the effects of treatment and prognostic factors, it is important to collect information on treatment (has the patient ever received medication for Pompe disease, and if so, which treatment and since/until when) as well as survival status (including date and cause of death).

4. Start and stop criteria for ERT in adult patients

A presentation about start and stop criteria applied in different countries initiated this session. This presentation included start and stop criteria used in the participating countries, as reported by the participants in the questionnaire, as well as published guidance from countries not represented in this workshop. This was followed by brief presentations from each country on the start and stop criteria applied in their country. In the subsequent group discussion, key questions included what minimal symptoms a patient should have to start treatment, whether severely affected patients should be started on treatment, the possibility of a trial period, stop criteria and whether ERT can be continued during pregnancy/lactation.

It was agreed that in order to start treatment, a patient needs to be symptomatic. Asymptomatic patients should be closely monitored. Severely affected patients can also start treatment, as long as they have some remaining muscle function. After starting treatment a patient is being evaluated using the clinical outcome measures described above. Discontinuation of treatment should be considered if there is no benefit of ERT. The full recommendation is being prepared for publication.

5. Summary and next steps

This workshop brought together a group of experts in the field of Pompe disease from nine European countries dedicated to work together to advance research on this disorder and provide expert opinion and guidance in clinical areas. Furthermore, the network will serve as an international contact point for health authorities to provide advice and expertise on Pompe disease.

During this first successful meeting of the network, two recommendations were developed for adult patients: a minimal dataset of outcome measures was agreed upon, as well as start and stop criteria for ERT. The minimal dataset is a first step towards sharing data to address specific research questions. Bringing together data from different countries will generate a much larger database than available in individual countries, allowing research into prognostic factors to progress.

The next steps of the network will be to discuss which specific research projects the network will focus on and how data can be shared for these. The consensus for the start and stop criteria for adults will be harmonized and published. Finally, outcome measures and the start and stop criteria for infants and children will be discussed.

6. List of participants (European Pompe Consortium, EPOC, members)

- Corrado Angelini, Venice, Italy
- Nadine A M E van der Beek, Rotterdam, The Netherlands
- Peter Van den Bergh, Brussels, Belgium
- Alexander Broomfield, Manchester, UK
- Claude Desnuelle, Nice, France
- Pieter A van Doorn, Rotterdam, The Netherlands
- Andreas Hahn, Giessen, Germany
- Michelle E Kruijshaar, Rotterdam, The Netherlands
- Robin Lachmann, London, UK
- Pascal Laforêt, Paris, France
- Eugen Mengel, Mainz, Germany
- Tiziana Mongini, Torino, Italy
- Wolfgang Müller-Felber, Munich, Germany
- George Padberg [ENMC], Nijmegen, The Netherlands
- Giancarlo Parenti, Naples, Italy
- Ignacio Pascual Pascual, Madrid, Spain
- W W M Pim Pijnappel, Rotterdam, The Netherlands
- Ans T van der Ploeg, Rotterdam, The Netherlands
- Mark Roberts, Manchester, UK
- Benedikt Schoser, Munich, Germany
- Beril Talim, Ankara, Turkey
- Antonio Toscano, Messina, Italy
- Wilma Treur, Baarn, The Netherlands
- John Vissing, Copenhagen, Denmark

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