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Muscular pathology

The French Pompe registry. Baseline characteristics of a cohort of 126 patients with adult Pompe disease

Registre Français de la maladie de Pompe. Caractérisation d'une cohorte de 126 patients adultes

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ABSTRACT

Pompe disease is a rare autosomal recessive muscle lysosomal glycogenosis, characterised by limb-girdle muscle weakness and frequent respiratory involvement. The French Pompe registry was created in 2004 with the initial aim of studying the natural history of French patients with adult Pompe disease. Since the marketing in 2006 of enzyme replacement therapy (alglucosidase alfa, Myozyme®), the French Pompe registry has also been used to prospectively gather the biological and clinical follow-up data of all adult patients currently treated in France. This report describes the main clinical and molecular features, at the time of inclusion in the French registry, of 126 patients followed up in 21 hospital-based neuromuscular or metabolic centres. Sixty-five men and 61 women have been included in the registry. Median age at inclusion was 49 years, and the median age at onset of progressive limb weakness was 35 years. Fifty-five percent of the patients were walking without assistance, 24% were using a stick or a walking frame, and 21% were using a wheelchair. Forty-six percent of the patients needed ventilatory assistance, which was non-invasive in 35% of the cases. When performed, muscle biopsies showed specific features of Pompe disease in less than two-thirds of the cases, confirming the importance of acid alpha-glucosidase enzymatic assessment to establish the diagnosis. Molecular analysis detected the common c.-32-13T > G mutation, in at least one allele, in 90% of patients. The French Pompe registry is so far the largest country-based prospective study of patients with Pompe disease, and further analysis will be performed to study the impact of enzyme replacement therapy on the progression of the disease.

RÉSUMÉ

La maladie de Pompe est une glycogénose musculaire rare, de transmission autosomique récessive, caractérisée par une faiblesse des ceintures, fréquemment associée à une insuffisance respiratoire. Le registre français de la maladie de Pompe a été créé en 2004, avec pour objectif initial d'étudier l'histoire naturelle des patients atteints de la forme adulte de la maladie de Pompe. Depuis la commercialisation de l'enzymothérapie substitutive par alglucosidase alfa (Myozyme®) en 2006, le registre français de la maladie de Pompe a aussi permis le recueil de données cliniques et biologiques pour l'ensemble des patients adultes actuellement traités en France. Ce travail décrit les principales caractéristiques cliniques et moléculaires des 126 patients adultes, qui sont suivis dans 21 centres de référence de maladies neuromusculaires ou métaboliques. Soixante-cinq hommes et 61 femmes ont été inclus dans le registre. L'âge médian à l'inclusion était de 49 ans ; l'âge médian du début de la faiblesse musculaire évolutive des ceintures était de 35 ans. Soixante-cinq pour cent des patients pouvaient marcher sans aide, 24 % avaient recours à l'aide d'une canne ou d'un déambulateur, et 21 % avaient recours au fauteuil roulant. Quarante-six pour cent des patients avaient recours à une ventilation assistée, avec une ventilation non invasive dans 35 % des cas. La biopsie musculaire montrait des anomalies caractéristiques de la maladie de Pompe dans moins de deux tiers des cas, lorsqu'elle avait été pratiquée, confirmant ainsi l'importance du dosage enzymatique de l'activité alpha-glucosidase acide pour établir le diagnostic. Les analyses moléculaires ont permis de détecter la présence de la mutation commune c.-32-13T > G sur au moins un des deux allèles chez 90 % des patients. Le registre français de la maladie de Pompe a permis de constituer la plus grande cohorte de patients

adultes atteints de cette maladie, et suivis de façon prospective, à l'échelle d'un pays. Des analyses complémentaires sont en cours afin d'étudier les effets de l'enzymothérapie substitutive sur l'évolution de la maladie.

1. Introduction

Pompe disease, or glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency in the activity of the lysosomal enzyme acid α-glucosidase (GAA). The clinical spectrum of this disease is extremely broad, varying from a severe infantile form leading to cardiorespiratory failure in the first months of life to adult-onset muscular manifestations (limb-girdle weakness and diaphragmatic paralysis) occurring in the third or fourth decade. Despite the fact that the infantile form was the first to be described (Pompe, 1932), the adult form is the most common one (Byrne et al., 2011; van der Ploeg and Reuser, 2008), representing more than 90% of diagnosed patients in France. Adults with Pompe disease typically present with limb-girdle muscle and axial weakness associated with diaphragmatic involvement (Engel, 1970; Laforêt et al., 2000). Disease progression is variable, but generally occurs over decades, potentially confining some patients to a wheelchair or causing them to require respiratory assistance (Hagemans et al., 2005; Pellegrini et al., 2005). Mean age for wheelchair or respiratory assistance has been estimated at around 50 years (Hagemans et al., 2005), and the major cause of death is respiratory failure.

The pathophysiology of this disease is particularly complex, with major cell disturbances caused by lysosomal glycogen accumulation and increased autophagy. Glycogen accumulation per se is not the only cause of cell dysfunction, and autophagy probably also has a major role in the pathogenic process, with recent works showing an autophagic build-up due to dysfunction of the endocytic and autophagic pathways in the muscle fibres (Raben et al., 2010). Autophagy seems to be more prominent in the juvenile and adult forms than in the infantile form of Pompe disease (Raben et al., 2010).

The prognosis for infantile Pompe disease has been modified considerably by enzyme replacement therapy (ERT), introduced 10 years ago (Kishnani et al., 2007, 2009). This treatment (alglucosidase alfa, Myozyme®), administered intravenously every other week, may improve cardiac and motor function and prolong the survival of affected babies. However at least one third of children do not respond to ERT, and ultimately die or do not reach a normal motor milestone.

In the adult form, results obtained from a double-blind, placebo-controlled study (LOTS) has shown a moderate but significant improvement in walking distance, and a stabilisation in sitting vital capacity after 18 months of treatment with alglucosidase alfa (Myozyme®) (van der Ploeg et al., 2010). Several open studies on older children and adults, published in recent years, have confirmed that ERT may improve or stabilise limb muscle strength and respiratory function (Strothotte et al., 2010; Bembi et al., 2010; Orlikowski et al., 2011; van Capelle et al., 2008, 2010; Angelini et al., 2011; Furusawa et al., 2012; Regnery et al., 2012), but data is still needed in order to better predict the long-term benefit of ERT.

Several guidelines reflecting consensus recommendations for the management and treatment of Pompe disease in various countries have also been published (Bembi et al., 2008; Llerena et al., 2009; Cupler et al., 2012). Their purpose was to define criteria for the diagnosis and management of specific symptoms, pre-treatment assessment, indications and monitoring of ERT. However, there is still a lack of global consensus today concerning the precise clinical criteria for ERT initiation and interruption in adults. Continuation of data gathering across the entire spectrum of Pompe disease, via national or international patient registries, is therefore warranted in order to assess the long-term safety and efficacy of ERT, and to formulate more precise guidelines for treatment. An international Pompe registry developed by Genzyme (www.pomperegistry.com) enrolled patients all over the world, but no data has yet been published on the efficacy and tolerance of treatment for patients with long-term follow-up (Byrne et al., 2011).

In order to improve our knowledge of Pompe disease, a national (French) Pompe registry has been created, with the collaboration of all French reference centres for rare neuromuscular and metabolic diseases. Below are the main clinical, pathological and molecular features of patients with adult-onset Pompe disease who have been included in the French Pompe registry since it was first set up.

2. Methods

2.1. Objectives of the French Pompe registry

Since 2004, we have been developing a national registry, with the aim of prospectively gathering the clinical, functional and biological data of all French patients with a diagnosis of Pompe disease confirmed by enzymatic and/or molecular analysis, whether treated or not. This registry has been qualified since 2008 by the French National Committee for Rare Diseases Registries (CNR-MR) supported by Inserm and institut national de veille sanitaire (InVS). Funding for the running of the registry has been provided by French Association against Myopathy (AFM), French Glycogenosis Association (AFG), Inserm, InVS, and Genzyme Corporation.

2.2. Registry design

The registry was developed (D.H.) using 4th Dimension language from 4D (http://www.4d.com) and the database is hosted on a secure server at Montpellier hospital. This database is managed by a clinical research assistant (N.T.) and a medical coordinator (K.L.) at the Myology Institute. It is accessed via the Internet from a key-locked program on users' computers. Data is entered into case report forms by participating doctors at French hospitals under the terms of a written agreement. Records concerning their own patients are available for use in clinical management. Anonymous data

are available to researchers subject to the approval of contributing clinicians and the steering committee.

2.3. Patients

Patients have been included in the registry if a diagnosis of Pompe disease has been proven either by enzymatic or genetic analysis (acid alpha-glucosidase deficiency or mutations in the GAA gene). They have been enrolled by 21 participating hospital-based centres. Informed consent has been signed by all patients, or by their parents if they were under the age of 18. Records are maintained without identifying patient information using code numbers. The study is compliant with national data protection requirements (Commission Nationale Informatique et Libertés).

2.4. Data collected

At the initial visit, patients' demographic information, history and current symptoms are recorded with emphasis on muscular, respiratory, cardiac and neurological symptoms. The results of muscle biopsy findings, biochemical and genetic analysis are recorded. All patients have been examined by a neuromuscular or metabolic diseases specialist, and muscular and respiratory functions are evaluated according to the resources of the investigating centre. Motor performance was assessed using manual muscle testing (MMT), timed tests (time to climb four steps, to rise from a chair, and to walk 10 m), Motor Function Measurement (MFM scale) and the 6-minute walking test (6MWT) for ambulant patients. The Motor Function Measure (MFM) consists of 32 brief tasks divided into three groups: standing/transfers, axial/proximal and distal tests. It has been validated in patients aged six to 60 years for various neuromuscular conditions (Bérard et al., 2005, 2010; Benaïm et al., 2010).

In some centres, muscle strength may also be evaluated by quantified muscle testing (QMT) and dynamometry (Biodex). Disability is assessed using functional grades (Brooke and Vignos scales) and the self-rated Rotterdam handicap scale. Respiratory evaluation includes the sitting and supine vital capacity (VC), and when possible maximum inspiratory and expiratory pressures. Laboratory tests include the assessment of CK and urinary GLC4 levels.

2.5. Statistical analysis

Descriptive data was expressed as frequencies (%) and mean ± standard deviation. The association between 6MWT, VC and MFM was examined using the Spearman's rank correlation coefficient. All tests were performed with R v.2.15.2. (R foundation, Vienna, Austria). A $P < 0.05$ was considered significant.

3. Results

3.1. Demography

One hundred and twenty-six patients were included in the French Pompe registry at the time of data extraction in September 2012 (Fig. 1). Sixty-one patients are women (48%) and 65 are men (52%). Parental consanguinity was noticed in only five patients. Forty-two patients (33%) reported affected siblings. Three siblings of three patients and eight siblings of two patients have been included in the registry so far. Several siblings were not included in the registry because they had died, were not being treated and were without follow-up, or were living in another country.

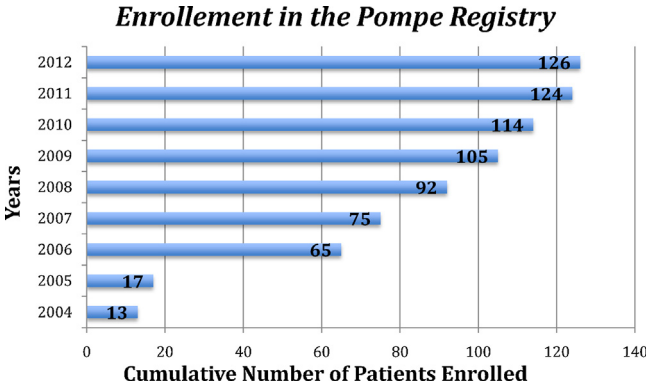

Fig. 1 – Cumulative inclusions in the Pompe registry since the creation of the registry.

Median age at inclusion was 49 ± 14 years (15–76) and age distribution was similar in men and women, with most of the patients being between the fourth and sixth decades (Fig. 2). Patients are followed up in 21 neuromuscular or metabolic reference centres distributed across France, with the largest cohort of patients (39%) being followed up in the Raymond-Poincaré and Pitié-Salpêtrière hospitals (Paris) (Fig. 3).

4. Diagnosis

4.1. Muscle biopsy

Ninety-three muscle biopsies were performed in an overall number of 84 patients (nine patients underwent two muscle biopsies). Muscle biopsy was performed in the quadriceps in

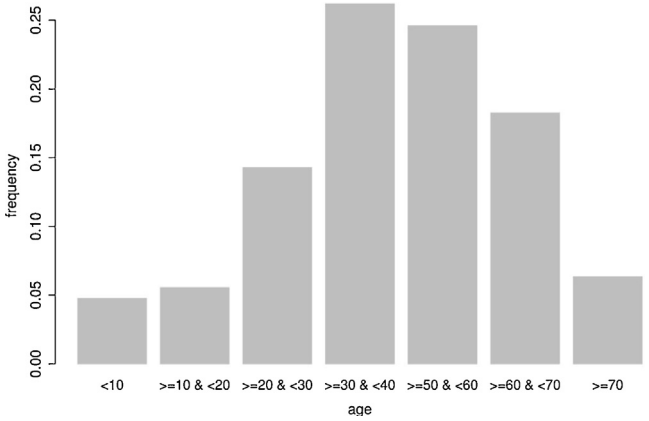

Fig. 2 – Age at inclusion in the registry. X axis: age range; Y axis: percentage of patients per decade.

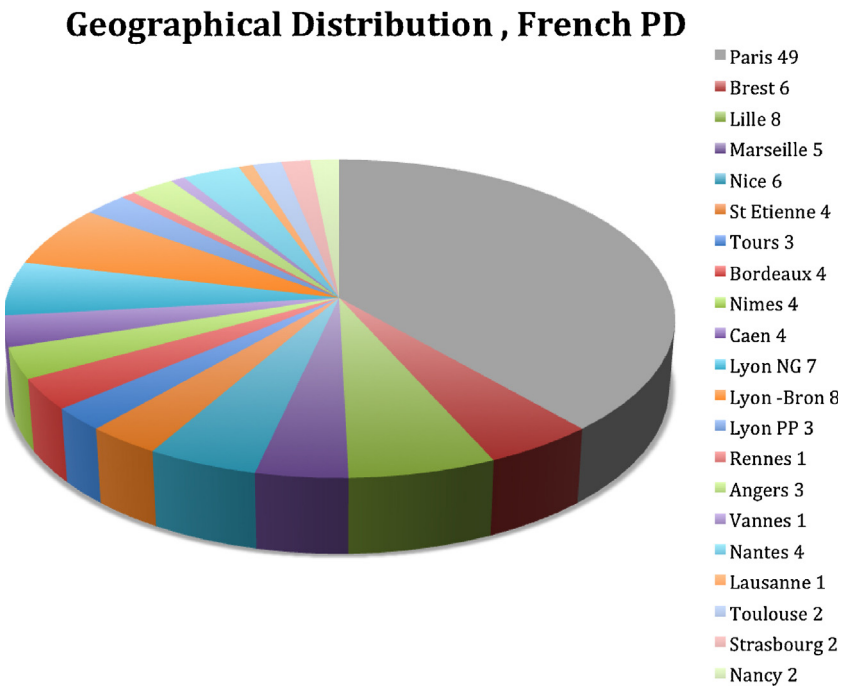

Fig. 3 – French Pompe registry enrolment by region.

49 cases, in the deltoid in 34 cases, and in another muscle in 10 cases. Vacuoles were observed in 63% of the muscle biopsies, and were most often observed in the quadriceps (67%) compared to the deltoid muscle (50%). An increase in PAS staining was observed in 54% of the muscle biopsies. Acid phosphatase activity was assessed in 65% of the muscle biopsies and increased activity was noticed in 49% of cases.

4.2. *Biochemical and molecular analysis*

Alpha-glucosidase deficiency was established through blood analysis in 93 patients, and confirmed by skin biopsy in 39 patients. The mean total creatine kinase level at inclusion was 546 IU/L ± U/L (n = 93; range: 61–2681). Nineteen patients (20%) had normal CK values (< 200 IU/L), 63 patients (68%) had CK values between 200 and 954 IU/L, and 11 patients (12%) had CK values between 1055 and 2681 IU/L.

GAA gene mutations were detected in 88 patients, and molecular studies are on-going for the other patients. Mutations on both alleles were known in 80 patients (64%). The majority of patients were compound heterozygotes or homozygous (3 patients) for the common intron 1 mutation (c.-32-13T > G) which was present in 79 cases (90% of patients). The second most common mutation was the "exon 18 deletion" c.2481 + 102-2646 + 31del, which has been detected in association with the c.-32-13T > G mutation in 11 patients. The so-called "Dutch mutation" c.525delT, was present in only four French patients.

4.3. *Initial course of the disease and presenting symptoms*

Most patients initially complained of progressive lower limb muscle weakness, either in isolation (57%) or in association with respiratory symptoms (20%). Respiratory insufficiency was the inaugural manifestation of the disease in nine cases (7%). An isolated hyper-CK-anemia led to the diagnosis in four patients. Other main reasons for initial consultation included episodes of low back pain, muscle fatigability or genetic counselling.

Mild muscle symptoms were often present since childhood. These symptoms included a delay in walking in five patients (4%) for whom this data has been recorded, with an average age of walking of 19 months. During childhood, 12 subjects (9%) had difficulties walking, 42 (34%) had difficulties running, and nine (7%) were exempted from sports activities at school. Scapular winging was reported in 16 patients (12%). Scoliosis was reported in 42 cases (33%), and was detected at an average age of 19 years. Two patients presented with rigid spine syndrome, the detailed clinical features of which having already been reported on one of them (Laforêt et al., 2010).

4.4. *Characteristics of limb muscle involvement at inclusion*

The median age at onset of progressive limb weakness was 35 years (range: 2–64 years). At the initial study visit, nearly all the patients were limited in terms of rising from a squatting position or from a chair, climbing stairs and standing from a supine position (Table 1). Sixty-nine patients (55%) walked without assistance, 30 patients (24%) were using aids such as a stick or a rollator and 27 patients (21%) needed a wheelchair (Fig. 4). Fourteen patients used their wheelchair full time, from the median age of 44 years (range: 14–73 years). Another 13 patients used a wheelchair only intermittently, from the median age of 47 years (range: 29–67 years).

The analysis of the 6-minute walking test, which was performed on 49 ambulatory patients at inclusion, showed a median walking distance of 340 m (range: 45–605 m). Results of

Table 1 – Functional impairment of the patients at the time of inclusion in the registry.

Functional impairment	Number of patients	Age of onset median (range)
Difficulties for rising from squatting	110 (89%)	40 (2–63) yrs
Difficulties for climbing stairs	112 (90%)	44 (2–71) yrs
Difficulties for rising from a chair	101 (83%)	42 (7–71) yrs
Difficulties for standing from supine position	110 (90%)	42 (2–73) yrs

the Motor Function Measurement (MFM scale) evaluation at the first visit ($n = 59$) were as follows: 79.1 ± 15.8 for the global score, 59.5 ± 27.6 for D1 (standing and transfers), 89.3 ± 14.5 for D2 (axial and proximal muscle function) and 98 ± 6 for D3 (distal muscle function). Standing activities and transfers were more strongly affected than limb-girdle function, as shown by the lower scores for D1.

The MFM correlated with the VC (R = 0.48, $P < 0.001$; D1 rho = 0.43, $P < 0.001$ (Fig. 5); D2 rho = 0.43, $P < 0.001$; D3 rho = 0.16, $P = 0.183$), but not with the change in VC from sitting to lying. The MFM also correlated strongly with the 6MWT (rho = 0.65, $P < 0.001$; D1 rho = 0.66, $P < 0.001$(Fig. 6)).

4.5. *Characteristics of respiratory involvement*

Fifty-eight patients (46%) needed ventilatory assistance at the time of inclusion. Forty-four patients (35%) needed non-invasive ventilation (NIV), and 14 patients (11%) were ventilated via tracheostomy. Non-invasive ventilation was only nocturnal for 31 patients and 13 patients also needed to be ventilated during the day. Invasive ventilation was nocturnal and diurnal for 13 patients.

The mean sitting VC, which was available for 111 patients, was 2.55 L (or 68% of normal value). The mean VC of patients who needed NIV was 1.93 L (or 50% of normal value) and the mean VC of non-ventilated patients was 3.11 L (or 84% of normal value). The VC was correlated with the 6MWT (rho = 0.34, $P = 0.0228$). Among the 44 patients who needed NIV, 31 were still ambulatory (19 walked without aid, and 11 walked with a stick) and 13 required a wheelchair. Half of the 14 patients who necessitated invasive ventilation were still able to walk.

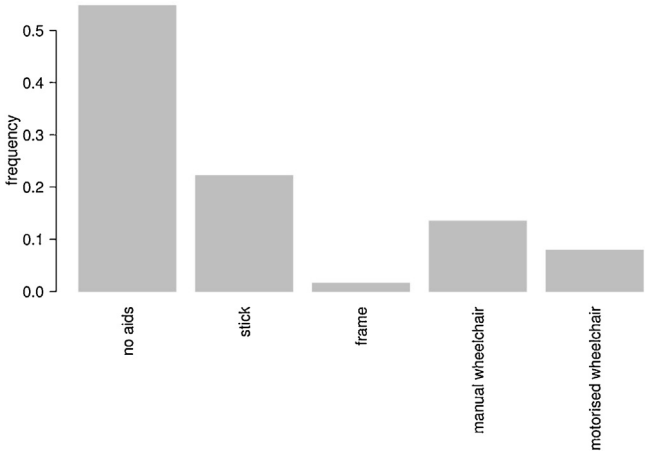

Fig. 4 – Levels of walking impairment of the patients included in the Pompe registry.

5. Discussion

Several publications have reported, for nearly 20 years, the description of clinical and molecular features of large series of patients with the adult form of acid alpha-glucosidase deficiency, also named acid maltase deficiency or ''late-onset Pompe disease'' (Wokke et al., 1995; Laforêt et al., 2000; Hagemans et al., 2005). Worldwide collections of clinical data have also been published recently, based either on self-assessment questionnaires (Güngör et al., 2011), or on data collection from the Pompe registry funded and administered by the Genzyme Corporation (Byrne et al., 2011). All these studies emphasised the significance of respiratory involvement occurring in the majority of patients, and thus the determination of the vital prognosis. On the other hand, these studies also showed the great variability of the clinical course among adult patients, and the difficulty in establishing prognostic factors at the time of diagnosis.

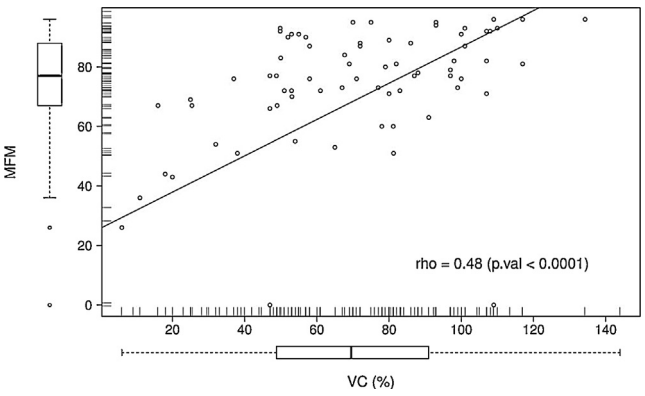

Fig. 5 – Correlation between Motor Function Measurement and vital capacity.

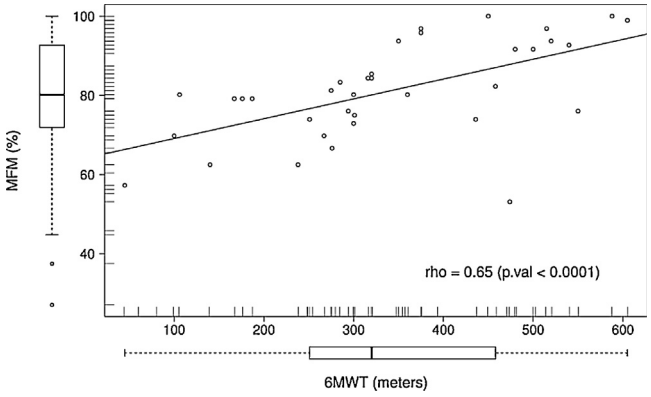

Fig. 6 – Correlation between Motor Function Measurement and 6-minute walking test.

In this paper, we describe the largest series of patients with adult Pompe disease from a single country with a prospective study of muscular and respiratory involvement. The French Pompe registry, which was initially designed to follow the natural history of patients, shifted rapidly towards becoming a major tool to assess the efficacy of ERT independently of the Pompe registry administered by the Genzyme Corporation. The analysis of the standardised clinical evaluations which are regularly performed on patients being treated with ERT is currently on-going.

As previously reported, the majority of patients experienced pelvic-girdle muscle weakness leading to the diagnosis of Pompe disease. Respiratory insufficiency was frequently detected at the time limb muscle weakness was diagnosed, but it could also be the initial symptom in some patients. Many patients presented with mild symptoms appearing during childhood, but they were generally not referred to a physician before the onset of a progressive muscle weakness during adulthood. Rigid spine syndrome was the initial clinical presentation in two patients, and in both patients the diagnosis of Pompe disease was established very late in the course of the disease due to the unusual clinical features and non-informative muscle biopsies (Laforêt et al., 2010).

A mild increase in CK levels, less than 1000 IU/L, was noticed in most patients; but this study also demonstrates that 20% of patients may have normal CK values and that conversely 12% of patients have CK values higher than 1000 U/L. Therefore, adult Pompe disease seems to be exceptionally associated with very high CK levels.

Muscle biopsy showed specific changes with vacuoles and excessive PAS staining in less than two-thirds of the patients, showing the limits of muscle biopsy in establishing a correct diagnosis. These results indicate the importance of performing a biochemical assessment of acid alpha-glucosidase activity to diagnose Pompe disease in an adult with proximal and axial muscle weakness, even when CK levels are normal.

Genetic analysis confirmed the high prevalence of the common c.-32-13T > G mutation, which was detected in at least one allele in 90% of patients who underwent molecular analysis. This mutation is the most frequent mutation globally (Byrne et al., 2011). Interestingly, 11 patients (12%) who have been genotyped harboured the exon 18 deletion which has been mostly reported in patients with the classical infantile form of Pompe disease. However, these 11 patients were not apparently more severely affected, with only one of them being wheelchair-bound, and 4/11 requiring nocturnal ventilatory assistance. Conversely, among the three patients homozygous for the c.-32-13T > G mutation, one was asymptomatic, but the other two had an important pelvic-girdle weakness and a severe respiratory involvement needing NIV in one. Therefore, our data do not allow to conclude to a more benign phenotype in these patients.

This study confirms the wide range of ages at the onset of lower limb-girdle muscle weakness in adults, with more common onset in the third decade, although many patients had experienced mild muscle symptoms since childhood. At the time of inclusion, more than half of the patients were walking independently, 25% needed a stick and less than 25% needed a frame or a wheelchair. Thus the lower limb weakness seems to be less severe than has been reported in a previous study performed on a Dutch population, in which only 37% of patients were walking without aid (Hagemans et al., 2005). Interestingly, the median walking distance of patients who remained able to walk was 340 m. This walking distance was similar to the distance walked by the patients who participated in the LOTS studies (332 m), showing in retrospect that the patients who participated in this study were a good reflection of the severity of the disease in the group of walking patients. The MFM scale, which has been also used to evaluate the level of impairment of muscle function, appears to be a useful tool, particularly with regard to the D1 dimensions, which evaluate standing activities and transfers. MFM provides a global measure of functional capacity, and importantly is applicable to patients who have lost ambulation. Therefore patients can be evaluated with the same measure throughout their illness. The good correlation between the MFM scores and 6MWT confirms the importance of this measurement in the follow-up of patients with Pompe disease.

Respiratory involvement was frequently observed in the French population, confirming the earlier studies. The main lesson of this study is that nearly half of the patients needed ventilatory assistance, with 35% of them having non-invasive ventilation and 11% of them being ventilated via tracheostomy. Severe respiratory problems therefore appear to be more frequent in our population as compared with the Dutch study, which reported 37% of patients using artificial ventilation (Hagemans et al., 2005). This variability in disease severity is more probably explained by a different genetic background, because the median age at the time of data collection was the same in the Dutch study (48.6 ± 15.6 years) and in the current study (49 ± 14 years).

This baseline analysis of the French Pompe registry supports a description of the main clinical features, along with the level of motor and respiratory impairment, of French patients with adult Pompe disease. This study adds additional information to the international Pompe registry, and will help to prospectively monitor the progression of the disease in all of the patients who have been included thanks to the French networks of rare neuromuscular and metabolic diseases reference centres. Further analysis of the data collected is on-going in order to detail the impact of ERT on the course of the disease.

Disclosure of interest

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The other authors declare that they have no conflicts of interest concerning this article.

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