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Methods of diagnosis of patients with Pompe disease: Data from the Pompe Registry

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ABSTRACT

Pompe disease is a rare, autosomal recessive disorder characterized by deficiency of lysosomal acid alpha-glucosidase and accumulation of lysosomal glycogen in many tissues. The variable clinical manifestations, broad phenotypic spectrum, and overlap of signs and symptoms with other neuromuscular diseases make diagnosis challenging. In the past, the diagnosis of Pompe disease was based on enzyme activity assay in skin fibroblasts or muscle tissue. In 2004, methods for measuring acid alpha-glucosidase activity in blood were published. To compare how diagnostic methods changed over time and whether they differed by geographic region and clinical phenotype, we examined diagnostic methods used for 1059 patients enrolled in the Pompe Registry in three onset categories (Group A: onset of signs/symptoms ≤12 months of age with cardiomyopathy; Group B: onset ≤12 months without cardiomyopathy and onset >1 year to ≤12 years; Group C: onset >12 years). Enzyme activity-based assays were used more frequently than other diagnostic methods. Measuring acid alpha-glucosidase activity in blood (leukocytes, lymphocytes, or dried-blood spot) increased over time; use of muscle biopsy decreased. The increased use of blood-based assays for diagnosis may result in a more timely diagnosis in patients across the clinical spectrum of Pompe disease.

1. Introduction

Pompe disease is a rare, autosomal recessive, neuromuscular disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA) that results in an accumulation of glycogen in lysosomes of many tissues, most notably skeletal, cardiac, and smooth muscle. Progressive accumulation of glycogen in these tissues leads to clinical debilitation, organ and system failure, and often death. Pompe disease manifests as a broad clinical spectrum with considerable variation in age of symptom onset, presenting signs and symptoms, and degree of severity and organ involvement, including cardiomegaly, hepatomegaly, and macroglossia [1,2]. The most severe form, classic infantile-onset Pompe disease, has an onset of signs and symptoms in the first few weeks to months of life and is characterized by progressive, hypertrophic cardiomyopathy, hypotonia, and death due to rapid cardiorespiratory failure, typically before 2 years of age [1,3,4]. Late-onset Pompe disease presents after 12 months of age (or as late as the 6th decade of life) and is characterized by a progressive, predominantly proximal limb and respiratory muscle weakness that is associated with significant morbidity and mortality [1,4–7]. While cardiac involvement is considered a defining feature of classic infantile-onset Pompe disease, it also has been reported in some late-onset patients [1,2,8]. However, more recent reports note cardiac dysfunction, suggesting that its presence has been underreported in late-onset patients. The reported cardiac involvement in late-onset patients is variable and includes rhythm disturbances, such as Wolff–Parkinson–White syndrome, electrocardiogram (ECG) abnormalities, and ascending aorta dilation [9–15]. Increased natural history data and the publication of various novel clinical presentations have expanded the known clinical spectrum of late-onset Pompe disease to include features such as arterial aneurysms, lingual weakness, oropharyngeal dysphagia, ptosis, and scoliosis [8,14,16–20]. Enzyme replacement therapy (ERT) is available as a specific treatment for Pompe disease. Patient outcomes improved in patients with the classic infantile-onset form of the disease when treatment with ERT is started early for these very young patients. Studies in patients with late-onset Pompe disease suggest that treatment with ERT can lead to improved outcomes or stabilization of disease progression [21–31]. With more widespread use of

Abbreviations: ACP, acid phosphatase; CRIM, cross-reactive immunologic material; DBS, dried blood spot; ECG, electrocardiogram; ERT, enzyme replacement therapy; GAA, acid alpha-glucosidase; IRB/EC, Institutional Review Board or Ethics Committee; MRI, magnetic resonance imaging; NBS, newborn screening; PAS, periodic acid-Schiff.

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newborn screening (NBS) programs, more will be learned about the early initiation of ERT in patients across the disease spectrum. Some challenges do remain because of unrecognized factors in a subset of patients who may not do well despite early start of ERT. In most cases, however, clinical benefits are maximal when treatment is initiated early. Therefore, with the availability of ERT and reported treatment benefits, accurate and early diagnosis of Pompe disease is important for all patients.

Demonstrating deficiency of GAA enzyme activity remains a standard for diagnosing Pompe disease. Current biochemical testing assays measure GAA enzyme activity in cultured skin fibroblasts, muscle biopsy tissue, or blood samples using dried blood spots (DBS) of whole blood on filter paper, purified lymphocytes, and mixed leukocytes [2,32–39]. Although measuring GAA activity is relatively easy, non-invasive, and inexpensive, significant delays in diagnosis remain [2,9,40–44]. The rarity of the disease, its variable clinical manifestations and phenotypes, and significant overlap of signs and symptoms with other neuromuscular diseases, make considering Pompe disease and ordering the diagnostic test a challenge [2,5,7,32,39].

Presented here is an overview of the diagnostic practices reported to the Pompe Registry. The methods used to diagnose Pompe disease, the change in use of the various diagnostic testing methods over time, and differences in methods used in the various geographic regions and patient subgroups for patients enrolled in the Registry will be reviewed. The ways in which these new technologies and clinical approaches are potentially leading to earlier and more accurate diagnosis of Pompe disease specifically for patients in the Registry and possibly for patients in general are discussed.

2. Methods

2.1. The Pompe Registry

The Pompe Registry, a long-term, multinational, observational program started in 2004 and sponsored and administered by Genzyme, a Sanofi company (Cambridge, MA), was designed to develop a better understanding of the natural history and outcomes of patients with Pompe disease. The Registry contains the largest collection of data on patients diagnosed with the disease. All patients with a confirmed diagnosis (documented GAA deficiency from any tissue source and/or documentation of two GAA gene mutations) of Pompe disease, regardless of age, clinical manifestations, or treatment status, can be enrolled by physician investigators worldwide. Patient participation in the Pompe Registry is voluntary. Clinical information is reported voluntarily to the Registry by participating physicians and healthcare team members involved in treating enrolled patients.

Each independent site obtains a patient's informed consent to submit his/her health information to the Registry and to use and disclose this information in subsequent aggregate analyses (journal articles, annual reports, education materials, and public health reports). Historically, each independent site was responsible for determining whether site-specific Institutional Review Board or Ethic Committee (IRB/EC) review is required for participation in the Registry in accordance with institutional policies and local laws and regulations. As of February 2013, the Pompe Registry protocol requires sites to submit to an IRB/EC.

2.2. Analysis description

We examined the methods used to diagnose Pompe disease in patients enrolled in the Pompe Registry and explored how use of diagnostic methods has changed over time and how they differ across geographic regions and by clinical phenotype, using a descriptive, cross-sectional analysis. All patients enrolled in the Registry were eligible for inclusion. The time to diagnosis from onset of symptoms of Pompe disease was not determined for this analysis, but is reported elsewhere [44].

A recommended Schedule of Assessments, developed by the Pompe Registry Board of Advisors, is provided as guidance. However, because assessments are performed according to individual patient needs and abilities at assessment time points and may be affected by regional clinical practices and standards of care, capabilities, and availability of testing resources, all patients may not have all recommended assessments completed. Also, data may not be recorded in the Registry for all measurements or assessments done for patients by their healthcare team. These assessment and reporting practices thus account for differences in the number of patients reported for various measures. Percentages reported for individual measures therefore reflect the percentages of patients who have the specific data reported in the Registry for individual measures and are not percentages of the total number of patients in the analysis.

Safety data are not collected by, or reported through, the Pompe Registry. Healthcare providers are advised to report adverse events and matters related to the safety of ERT directly to the Genzyme Global Pharmacovigilance and Epidemiology Department.

Data collected through the Pompe Registry are entered into a database, analyzed, and reviewed for missing data points, incomplete information, and discrepancies with previously submitted data by members of the Registry staff. If necessary, issues are resolved with the site. Site visits are conducted periodically to review the quality of the data entered into the Registry database. All data management and analyses occur in a validated computing environment.

For this analysis, three onset categories based on patient age at first sign or symptom onset and evidence of cardiomyopathy (as reported by echocardiogram, or as an enlarged heart on chest X-ray or ≥ 1 enlarged atria or ventricles on an electrocardiogram in the absence of echocardiogram results) were identified: Group A (onset of signs or symptoms ≤ 12 months of age with cardiomyopathy); Group B (onset of signs or symptoms ≤ 12 months without cardiomyopathy and onset of signs or symptoms >1 year to ≤ 12 years); and Group C (onset of signs or symptoms >12 years). Age at sign or symptom onset was reported in months for patients in Group A and in years for Groups B and C. The year of diagnosis for patients was grouped into pre-2000 and 2-year strata after 2000 to evaluate changes in diagnostic methods used over time.

The presenting sign or symptom class was determined by the reported signs or symptoms occurring within 1 month of the first recorded symptom in patients in Group A, and within 1 year for patients in Groups B and C.

The diagnostic methods used were categorized as follows: all possible combinations of DNA, enzyme activity, and “other” testing, or as unknown/missing for patients without a reported method of diagnosis or for whom the method was “unknown.” The enzyme diagnostic category includes GAA enzyme activity testing methods that are reported as DBS, other blood-based (lymphocyte and leukocyte), fibroblast, muscle, or unknown/missing. “Other” includes all write-in responses that could not be recoded to DNA or enzyme analysis, such as muscle biopsy for histologic examination, which involves the microscopic evaluation of muscle tissue to identify histologic characteristics of abnormal glycogen accumulation. This differs from enzyme assays that measure GAA enzyme activity in a sample of muscle tissue [2]. Patients may have had more than one type of assay used in reaching a diagnosis and, therefore, could have more than one assay type reported.

For analysis of single versus multiple methods of diagnosis, “single” refers to use of a single enzyme assay method, DNA analysis only, or a single reported “other” method only, and “multiple” includes any combination of enzyme activity assay, DNA analysis, or other methods or more than one enzyme methods.

We used descriptive statistics to analyze data according to demographic and clinical characteristics of patients in the Registry who were included in this analysis. Percentages were calculated for the diagnostic methods used among patients for each independent