The natural course of non-classic Pompe’s disease; a review of 225 published cases

Abstract Pompe's disease is a neuromuscular disorder caused by deficiency of lysosomal acid α-glucosidase. Recombinant human α-glucosidase is under evaluation as a therapeutic drug. In light of this development we studied the natural course of cases not fitting the definition of classic infantile Pompe's disease. Our review of 109 reports including 225 cases shows a continuous spectrum of phenotypes. The onset of symptoms ranged from 0 to 71 years. Based on the available literature, no criteria to delineate clinical sub-types could be established.

A common denominator of these cases is that first symptoms were related to or caused by muscle weakness. In general, patients with a later onset of symptoms seemed to have a better prognosis. Respiratory failure was the most frequent cause of death. CK, LDH, ASAT, ALAT and muscle glycogen levels were frequently but not always elevated. In most cases a muscle biopsy revealed lysosomal pathology, but normal muscle morphology does not exclude Pompe's disease. In 10% of the cases in which the enzyme assay on leukocytes was used, a normal α-glucosidase activity was reported.

Data on skeletal muscle strength and function, pulmonary function, disability, handicap and quality of life were insufficiently reported in the literature. Studies of non-classic Pompe's disease should focus on these aspects, before enzyme replacement therapy becomes generally available.

Key words alpha-glucosidase · glycogenosis · lysosomal storage disorder · muscular dystrophy

Introduction Pompe's disease is a metabolic myopathy caused by the deficiency of acid α-glucosidase needed for the degradation of lysosomal glycogen [33, 50, 51]. With studies on enzyme therapy well underway it becomes increasingly important to recognise signs and symptoms of the disease properly and to establish the diagnosis without delay [125, 127, 132]. Accurate knowledge on the natural course of the disease is further required to set endpoints for pivotal clinical trials and to decide in each individual
case at what moment enzyme therapy should be started once it is generally available.

In 1932 J. C. Pompe presented the first case report. It concerned a patient with a hypertrophic cardiomyopathy and progressive generalised muscle weakness [97]. The child died at eight months of age. This severe form of the disease is quite well delineated [24, 30, 32, 126]. Symptoms start at a median age of 1.6 months, patients die at a median age of 6–8 months, a hypertrophic cardiomyopathy is characteristically present, and developmental milestones like rolling-over, sitting and standing are not achieved. This is the classic infantile form of Pompe's disease.

Milder forms were described later. These were called muscular variant, nontypical infantile, childhood, juvenile, adolescent, adult and late-onset forms of Pompe's disease. Guidelines for sub-classification are not clearly set [25, 37, 39, 48, 50, 53, 54, 70, 90, 115, 133, 135]. This review depicts the features of 225 cases of Pompe's disease that do not fit the description and course of the classic infantile form, as extracted from 109 publications.

Methods

We included all case reports identified via Pubmed by a search for "Late(-)onset Pompe's disease", "Acid Maltase deficiency", "Glycogenosis type II/2", "Glycogenosis type 2a" and "Childhood –", "Juvenile –", "Adult –" and "Non(-)typical Infantile Pompe's disease". Case reports cited in the collected articles, and case-reports not identified via Pubmed were added to the list. Articles written in English, French, German or Dutch were included. Excluded were publications lacking clinical information, cases with normal acid α-glucosidase activity in muscle tissue or fibroblasts and cases described as Danon's disease [10, 15, 19, 60, 61, 94, 124]. We further excluded all cases that fulfilled the criteria of classic infantile Pompe's disease, which were earlier included in a review on the natural course of infantile Pompe's disease [126]. This led to a collection of 225 cases in 109 articles [1–3, 5–9, 11, 12, 16–18, 20–23, 25–29, 31, 34–49, 52–59, 62–85, 87–93, 95, 96, 98, 99, 100–102, 106–123, 128–130, 133–135].

In order to identify subtypes of Pompe's disease we grouped the patients by age at onset of symptoms, more or less following the terminology 'non-typical infantile', 'childhood', 'juvenile' and 'adult'. This led to a division in four groups: < 1 year, from 1–6 year, from 6–18 years, and ≥18 years. We then compared the patients in these four groups with regard to general characteristics, clinical manifestations and course of disease, enzymatic, histological and other laboratory findings. If particular symptoms or signs were not reported, they were scored as negative. Laboratory findings were scored as abnormal or normal, and by exact value when reported by the authors.

The data were analysed using SPSS 10.1. We used descriptive statistics and frequencies for all calculations in this report. Data are presented as medians, unless otherwise indicated.

Results

General overview of the study population

We collected 225 case reports of patients with Pompe's disease who did not have the classic infantile phenotype. The case reports originated from 19 countries, mostly from the United States (30%), France (16%) and The Netherlands (15%), but also for example from Japan (6%) and South Africa (2%). The distribution of age at time of description is presented in Fig. 1. Forty-three percent of the patients were female. Remarkably, when the patients were subdivided into groups based on age at onset, there was a predominance of affected males in the younger age groups. Although the medians for doctor's delay, age at description, age at start of ventilation and age at death differed between the four groups, the ranges overlapped considerably (Table 1). For example, one patient with symptoms in the first year of life was diagnosed at the age of 17 and was still alive at the age of 28. Another patient who experienced first symptoms between 6 and 18 survived beyond 61 years. The oldest patient (71 years) presented with symptoms at the age of 68.

First symptoms were described for 207 of the 225 cases (Fig. 2). Most often mentioned were symptoms and signs related to muscle weakness (80%). These comprised abnormal walking, difficulty with climbing stairs, delayed motor development and hypotonia. Second most frequent were respiratory problems; these were described in 11% of the cases. Respiratory failure was the presenting symptom in 2% of the cases.