CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

Infantile and later-onset paediatric Pompe disease (glycogen storage disease type II)

PROTOCOLS

Principal investigators

Craig Campbell, MD, Department of Neurology, Paediatrics, University of Western Ontario, London Health Sciences Centre 800 Commissioners Rd. E., London ON, N6A 5W9; tel.: 519-685-8332; fax: 519-685-8350; craig.campbell@lhsc.on.ca

Hugh McMillan, MD, Division of Neurology, Paediatrics, Children's Hospital of Eastern Ontario; hmcmillan@cheo.on.ca

Eugenio Zapata Aldana, MD, Genetics, Department of Neurology Paediatrics, London Health Sciences Centre, 800 Commissioners Rd. E., London ON, N6A 5W9; tel.: 519-685-8332; fax: 519-685-8350; Eugenio.zapataaldana@lhsc.on.ca

Co-investigators

Catherine Brunel-Guitton, MD, CHU Sainte-Justine
Pranesh Chakraborty, MD, University of Ottawa
John Mitchell, MD, McGill University
Johannes Roth, MD, University of Ottawa
Tony Rupar, MD, University of Western Ontario
Mark Tarnopolsky, MD, McMaster University
Lesley Turner, MD, Janeway Children's Health and Rehabilitation Centre

Background

Pompe disease, also known as glycogen storage disease type II (GSD-II), is an inherited, autosomal recessive disease that results from abnormal lysosomal storage of glycogen in body tissues. Children with Pompe disease have a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). The clinical spectrum ranges from the severe, infantile-onset form, to the milder juvenile phenotype that develops later in childhood. The variability in disease severity is related to the amount of residual GAA enzyme activity in muscle. GAA enzyme activity of <1–3% of normal controls is associated with classic infantile-onset Pompe disease. Infants exhibit severe hypotonia and weakness, cardiomyopathy, poor feeding, and respiratory failure. Children with untreated, classic infantile-onset Pompe disease will typically not survive beyond 12 months old, with death most commonly attributable to complications of cardiorespiratory failure (i.e., progressive left ventricular outflow obstruction). Among patients with the non-classic variant of infantile-onset Pompe disease, death results from ventilatory failure in early childhood. Higher levels of residual GAA activity (i.e., 3–30% normal values) is associated with milder and later-onset forms of the disease that can present anytime in childhood or adulthood. Most patients will present with muscle weakness predominantly in a proximal or limb-girdle (pelvic > scapular) pattern. Children are found to have high

serum creatine kinase (CK) levels and/or exercise intolerance due to respiratory insufficiency. CK levels may or may not be normal in adults.

Many patients with late-onset Pompe disease experience long delays until diagnosis. A recent report identified a mean of 4.1 years delay from symptom-onset until diagnosis.[1] In a large cohort of adult patients with an unclassified limb-girdle muscular dystrophy (LGMD) or an undiagnosed mildly elevated serum CK (i.e., 1–8 times the upper limit of normal), 7.5% of LGMD patients and 2.5% of patients with persistent idiopathic elevation of serum CK were found to have Pompe disease.[2] This is particularly important in light of the fact that enzyme replacement therapy can improve cardiomyopathy, ventilator function, and prolong survival in patients with infantile Pompe disease[3], and also improve muscle strength, pulmonary function, and survival in patients with later-onset Pompe disease.[4] A pilot newborn screening study has demonstrated that early treatment with GAA is critical in the treatment of infants with Pompe disease and has highlighted the need for early diagnosis[5], and early treatment.[6]

Methods

Through the established methodology of the Canadian Paediatric Surveillance Program (CPSP), paediatricians and paediatric subspecialists will be asked each month if they have any children or adolescents they are currently following in their practices with Pompe disease. This includes both **confirmed** incident and prevalent cases (i.e., patients with newly diagnosed Pompe disease AND patients with long-standing Pompe disease). Respondents who identify cases will be asked to complete a detailed questionnaire for each case.

Case definition

Report any patient (new or previously diagnosed) of less than 18 years old meeting the following criteria:

1. **Genetic criteria:** Pathogenic mutations affecting both *GAA* genes (encodes the acid alpha-glucosidase protein) as determined by sequence analysis or deletion/duplication analysis

   AND/OR

2. **Biochemical criteria:** Measurement of acid alpha-glucosidase (GAA) enzyme activity performed on one or more of:
   - Dried blood spot GAA enzyme activity assay
   - Whole blood GAA enzyme activity assay
   - Skin biopsy (fibroblast culture) GAA enzyme activity assay
   - Muscle biopsy GAA enzyme activity assay

Exclusion criteria
Clinical evidence of proximal muscle weakness without genetic or biochemical confirmation of disease

Objectives

1) Characterize the presenting symptoms and clinical characteristics of infantile and juvenile-onset paediatric Pompe disease
2) Determine the minimum incidence and minimum prevalence of infantile-onset and juvenile-onset paediatric Pompe disease in Canadian children and adolescents
3) Compare minimum incidence and minimum prevalence of infantile- and juvenile-onset paediatric Pompe disease by comparing the number of cases reported to the

CPSP with those reported to patient-initiated disease registries (e.g., the Canadian Neuromuscular Disease Registry)

4) Raise awareness among Canadian paediatricians about infantile and juvenile-onset Pompe disease in Canadian children and adolescents so that the disease may be considered in the differential diagnosis for children presenting with proximal weakness, hypotonia, respiratory insufficiency, and/or high serum CK

Duration

October 2017 to September 2019

Expected number of cases

It is estimated that there will be between 48–148 patients with Pompe disease (GSD-II) that will be reported to the CPSP over the two-year study timeframe.

The overall incidence of Pompe disease (GSD-II) is estimated to be approximately: 1 in 33,000 in Taiwan[7]and 1 in 40,000 in The Netherlands.[8] The frequency of disease has been estimated to be approximately 1 in 138,000 for the infantile type and 1 in 57,000 for later-onset (juvenile and adult) disease.[8]

In 2015, Statistics Canada reported the population of Canadian children (0 to 14 years old) to be approximately 5,754,477.[9]

Martiniuk et al. (1998) calculated the carrier frequency of GAA mutation among adults in New York City, and used that data to estimate the total number of patients with GSD-II living in the United States, which they reported as between 1,900 (480 juvenile cases plus 1,400 adult cases) and 3,000 (680 juvenile cases and 2,300 adult cases).[10]

Based upon the disease frequency in other nations and disease prevalence estimates calculated from the United States carrier frequency data, it is predicted that there are between 48–148 children and adolescents in Canada with Pompe disease. Given the delay to diagnosis for individuals with later-onset Pompe disease, the actual number reported may be smaller.

Ethical approval

Research Ethics Board at London Health Sciences Centre

Funding

The CPSP is a joint project of the Public Health Agency of Canada (PHAC) and the Canadian Paediatric Society (CPS), funded by PHAC and managed by the CPS. Funding for this specific surveillance project was provided through an unrestricted grant by Genzyme.

Analysis and publication

Data will be summarized using descriptive statistics. Data analysis will be completed within six months of the end of this CPSP study. Annual and final reports will be published in the *CPSP Results* and circulated to all CPSP participants. Completed study results will be presented at national and international scientific meetings and submitted for publication in scientific peer-reviewed journals. Knowledge translation will include comparative data of minimum disease prevalence and will be distributed to all provinces and territories to encourage the addition of Pompe disease to the list of diseases for newborn screening. Presentations will also be offered to community partners, the

Canadian Association of Pompe, and Muscular Dystrophy Canada.

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