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Hypothyroidism in late-onset Pompe disease

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ABSTRACT

Purpose: In Pompe disease, a deficiency of acid α-glucosidase enzyme activity leads to pathologic accumulation of glycogen in tissues. Phenotype heterogeneity in Pompe includes an infantile form and late-onset forms (juvenile- and adult-onset forms). Symptoms common to all phenotypes include progressive muscle weakness and worsening respiratory function. Patients with late-onset forms of Pompe disease commonly complain of chronic fatigue and generalized muscle weakness prior to being diagnosed with Pompe disease, and this may lead to consideration of hypothyroidism in the differential diagnosis. This study aimed to evaluate the prevalence of hypothyroidism in the adult-onset form of Pompe disease.
Methods: Electronic chart review was performed at the Advanced Therapies Clinic at the University of Minnesota Medical Center (UMMC) to identify patients with late-onset Pompe disease. The identified charts were reviewed for a co-diagnosis of hypothyroidism. A query was made to the clinical data repository at UMMC searching diagnosis ICD9 code 244.9 (hypothyroidism not otherwise specified) and/or presence of levothyroxine from 2011 to 2014 in patients 18 years of age and older.
Results: The clinical data repository found a prevalence of hypothyroidism of 3.15% (56,072 of 1,782,720 patients) in the adult patient population at UMMC. Ten adult patients with Pompe disease were identified, five with the diagnosis of hypothyroidism (50%, 95% CI: 23.7, 76.3, $p < 0.001$ compared with the general UMMC adult population).
Conclusions: Hypothyroidism was found at a higher prevalence in patients with late-onset Pompe disease compared to the general adult population at UMMC. Studies in larger populations of patients with Pompe disease would be needed to confirm an association of Pompe disease and hypothyroidism. Challenges include finding an adequate sample size, due the rarity of Pompe disease.

1. Introduction

Pompe disease is a rare disease, estimated to occur in approximately 1:150,000 live births (Sarafoglou, K. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw Hill, 2009; page 728). It is inherited through an autosomal recessive pattern and caused by mutations of the acid α-glucosidase (*GAA*) gene localized at chromosome 17q25.2–q25.3, resulting in absence or reduced enzyme activity of acid α-glucosidase (EC 3.2.1.20) [1–3]. Acid α-glucosidase is a ubiquitously expressed glycoprotein responsible for the hydrolysis of α-1.4 and α-1.6 bonds of glycogen. As a storage form of glucose, glycogen is a large branched polymer of glucose residues that can be released in catabolic states. Deficiency of acid α-glucosidase in Pompe disease leads to the pathologic accumulation of glycogen in the lysosomes and between the myofibrils, predominantly in the skeletal, cardiac and smooth muscle.

The most severe form of Pompe disease, infantile Pompe disease, presents within the first few months of life with symptoms of hypotonia, cardiomegaly, macroglossia, hepatomegaly and progressive muscle weakness [1–3]. Death occurs usually before 1 year of age in patients with the infantile form of Pompe disease. Later-onset forms of Pompe disease may present between early to late childhood (juvenile-onset) and well into adulthood (adult-onset), with varying severity of muscle weakness. In late-onset Pompe disease, the lower limbs are usually more affected than upper limbs. Cardiomyopathy is uncommon in later-onset forms of Pompe disease [1–4].

Patients with later-onset Pompe disease often develop slowly progressing proximal and paraspinal muscle weakness. They may suffer

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from frequent respiratory infections, sleep disordered breathing and respiratory failure. Chronic fatigue is common [4]. The progressive nature of the myopathy, respiratory involvement, and chronic fatigue in late-onset Pompe disease leads to varying degrees of disability, eventually requiring wheelchair and ventilator assistance for most patients. Elevated creatine kinase (CK) levels are typical [2,3]. Delayed or misdiagnosis is common due to the rarity of Pompe disease, and the similarity of presenting symptoms of late-onset Pompe disease to other muscular myopathy diseases [3,4]. During the diagnostic work-up, hypothyroidism may be considered as part of the differential diagnosis, due to patient complaints of fatigue and weakness.

Pharmacotherapy consultation services at the University of Minnesota Medical Center (UMMC) Advanced Therapies Lysosomal Disease Clinic noted that a seemingly high number of late-onset Pompe patients were taking levothyroxine and carried a diagnosis of hypothyroidism. This observation raised the question of the prevalence of hypothyroidism in late-onset Pompe disease and led to exploration of the prevalence of hypothyroidism in late-onset Pompe patients compared to the adult patient population as a whole, at UMMC.

2. Methods and materials

2.1. Study population

The University of Minnesota Institutional Review Board approved this study. Inclusion criteria included diagnosis of late-onset Pompe disease confirmed by enzyme assay and/or genetic testing. There were no exclusion criteria for this study.

2.2. Study design

2.2.1. Pompe disease case-finding

Electronic chart query of the clinical data repository for the adult patient population at UMMC was performed to identify patients with Pompe disease (ICD9 code 271.0). The identified charts were retrospectively reviewed for confirmation of Pompe disease by enzyme assay and genetic testing. The charts of adult patients with Pompe disease were retrospectively reviewed for co-diagnosis of hypothyroidism, all thyroid function test results and/or thyroid hormone treatment. Hypothyroidism was established by either documented historical reference or treatment, as defined by the treating physicians. Where possible, thyroid tests were reviewed to confirm the original diagnosis.

2.2.2. Hypothyroidism case-finding

To evaluate prevalence of hypothyroidism in the general adult patent population at UMMC, an electronic chart query was made to the clinical data repository at UMMC searching diagnosis ICD9 code 244.9 (hypothyroidism not otherwise specified) and/or the medication levothyroxine in patients 18 years of age and older from 2011 to 2014.

2.2.3. Statistical analysis

For comparison of the prevalence of hypothyroidism in the late-onset Pompe disease population to the general UMMC population query, mean and standard deviation for continuous variables (age at Pompe diagnosis, age at thyroid function test, TSH, and free T4) and frequency for categorical variables (sex, *GAA* genotype, thyroid treatment, dose of medication) of patient characteristics were summarized. Confidence intervals for proportions were determined by inverting the score test. All analyses were performed using R v3.1.1.

3. Results

3.1. Hypothyroidism in Pompe disease

Ten adult patients with Pompe disease were identified, including five males and five females (Table 1). The patients identified were from seven different families. Seven different *GAA* mutations were present in the group.

Nine of the patients were diagnosed with Pompe disease during adulthood. One patient was diagnosed at age 15 years. The age at diagnosis of Pompe disease ranged from 15 to 66 years.

Five of the ten patients with Pompe disease (50%, 95% CI: 23.7, 76.3) carried a diagnosis of hypothyroidism (subjects 6–10) and were on treatment with levothyroxine.

The age at the time of diagnosis of hypothyroidism in the patients with Pompe disease ranged from 23 to 57 years. Four of the five hypothyroid Pompe patients were female. Three of the five patients were diagnosed with hypothyroidism prior to receiving a diagnosis of Pompe disease.

Pre-treatment thyroid function tests were available for three of the five hypothyroid Pompe patients. All had TSH less than or equal to 10 μIU/ml.

Two of the hypothyroid female subjects were from the same family (# 8 and 9). A specific *GAA* genotype was not suggested in the hypothyroid cohort, though the sample size was insufficient to draw conclusions on this. Additional demographic information, including specific Pompe genotype and levothyroxine dose, can be found in Table 1.

3.2. Hypothyroidism in the general population

The search of the clinical data repository at UMMC identified 56,072 patients with ICD9 code 244.9 out of 1,782,720, an estimated hypothyroid prevalence of 3.15%, CI: (3.12%, 3.17%). The search identified 76,384 patients with the medication levothyroxine out of 1,782,720, an estimated prevalence of 4.28% CI: (4.26%, 4.31%). Combining search criteria ICD9 code 244.9 and levothyroxine identified 49,530 out of 1,782,720 patients, an estimated hypothyroid treatment prevalence of 2.78% CI: (2.75%, 2.80%).

There was a higher prevalence of hypothyroidism in the study population of late-onset Pompe disease compared to the general adult UMMC population based on ICD9 code 244.9 and/or levothyroxine treatment ($p < 0.001$).

4. Discussion

Incidental observation of several cases of hypothyroidism among those being seen for Pompe disease led to a further evaluation of the possible association of these co-morbidities and comparison to the prevalence in general patient populations. The findings suggest the possibility of a previously unrecognized, non-random association. This is the first study to uncover the possible association between hypothyroidism and late-onset Pompe disease. Fifty percent of the ten adult-onset Pompe patients at UMMC have been treated for hypothyroidism, a significantly higher rate compared to estimates from a query of the UMMC electronic medical record general adult population. The prevalence of hypothyroidism in the adult patients with Pompe disease at UMMC is also much higher than what is reported from general populations in the medical literature [5–9] where the rate is estimated in the range from 0.2 to over 24%, depending on age, sex and iodine status, with US averages most typically cited in the 4–5% range [6,8]. The degree of hypothyroidism was mild where it could be verified in the adult patients with Pompe disease at UMMC. In three of the five cases (60%) the diagnosis of hypothyroidism preceded the diagnosis of Pompe disease.

Although this study did not evaluate patients with infantile Pompe disease, the similarity of clinical features of hypothyroidism and infantile Pompe disease has been noted [10]. Hypothyroidism also shares a number of clinical features with presenting symptoms of late-onset Pompe disease, including fatigue, cramping, reduced exercise tolerance, muscle weakness, and high CK levels [3,4,11]. These commonalities suggest the diagnosis of Pompe disease should be considered, along with

Table 1
Adult-onset Pompe disease patient demographics. The age at thyroid function tests correlates to the age at diagnosis of hypothyroidism for the hypothyroid subjects.

Patient demographics									
Subject number	Family number	Sex (M/F)	Age at Pompe diagnosis (years)	*GAA* genotype	Age at thyroid function testing (years)[a]	TSH (mU/L)	Free T4 (ng/dL) (normal 0.76–1.46 ng/dL)	Thyroid treatment	Dose of medication
1	1	M	34.1	c.-32-13T>G, c.525delT	52.8	1.98	1.61	N/A	N/A
2	2	M	15.0	c.1754G>A, c.2560C>T	16.9	4.74	1.34	N/A	N/A
3	3	F	46.6	c.-32-13T>G, c.2481 + 102_2646-31del	51.1	2.04	1.16	N/A	N/A
4	4	M	65.7	c.692 + 5G>T, c.1076-22T>G	72.4	4.12	0.93	N/A	N/A
5	4	M	57.0	c.692 + 5G>T, c.1076-22T>G	57.0	4.46	1.28	N/A	N/A
6	4	M	59.5	c.692 + 5G>T, c.1076-22T>G	56.7	8.21	1.08	Levothyroxine	88 mcg daily
7	5	F	31.3	IVS1-S3T>G, c.1128_1129delGGinsC	Unknown	Not available	Not available	Levothyroxine	137 mcg daily
8	6	F	52.0	c.1478>T, c.525delT	53.0	10.20	0.79	Levothyroxine	75 mcg daily
9	6	F	50.9	c.1478>T, c.525delT	49.8	6.80	Not available	Levothyroxine	75 mcg daily
10	7	F	35.5	c.-45T>G. 538 bp deletion c2481 + 102 - c2646 + 36	23.1	Not available	Not available	Levothyroxine	125 mcg daily

[a] The age at thyroid function testing is also the age of diagnosis of hypothyroidism for the hypothyroid patients.

hypothyroidism, in the diagnostic work-up for adult patients presenting with worsening muscle weakness and fatigue.

A few earlier studies suggested that hypothyroidism and Pompe disease share some biochemical features at a cellular level. Hurwitz et al. (1970) reported reduced α-glucosidase activity in hypothyroid myopathy [12] and Spiro et al. (1970) reported intramuscular glycogen accumulation in patients with hypothyroidism [13]. Hui et al. (1985) noted thyroid follicular cell accumulation of glycogen by light microscopy at autopsy in patients with Pompe disease [14].

Much remains to be learned about the possible role(s) of lysosomal enzyme functioning in thyroid tissue. Studies of thyroglobulin hormone interaction with the lysosomal enzymes, cathepsin B and cathepsin K, have helped increase understanding of this relationship. Thyroglobulin, a glycoprotein synthesized by the thyrocytes, is stored in a colloid fluid found in small globular sacs, or follicles, of the thyroid gland. Thyroglobulin serves as a scaffold protein for the synthesis of thyroid hormones (e.g., thyroxine and triiodothyronine) and for the storage of iodine. When thyroxine is needed, thyroglobulin is brought by endocytosis from the colloid filled follicle sacs into the thyroid follicle cells that line the follicles. In the follicle cells, the thyroglobulin then binds to a lysosome to form a secondary lysosome where lysosomal protease enzymes, cathepsin B and cathepsin K, release thyroxine and triiodothyronine from the thyroglobulin [15,16].

Mouse knockout models of Pompe disease have shown that accumulation of glycogen affects trafficking of enzymes to the lysosomes [16–18]. Moreover, the mobility and communication between autophagosomes, lysosomes and endosomes decrease with continued Pompe disease progression [17,18]. Thus, a possible consideration is that the activity and function of the lysosome and lysosomal enzyme trafficking in the thyroid gland tissue, may be impaired by the accumulation of glycogen and autophagic build-up in patients with Pompe disease.

Importantly, endocrine dysfunction has been observed in patients with other lysosomal diseases [19]. Hypothyroidism and subclinical hypothyroidism have been documented to occur more frequently in patients with Fabry disease, a lysosomal disease in which globotriaosylceramide is accumulated in tissues and the thyroid gland [19,20]. Moreover, thyroid function has been observed to improve in patients with Fabry disease in response to enzyme replacement therapy (ERT) [21]. To date, the impact of alglucosidase alfa, an FDA-approved intravenous enzyme replacement therapy for treatment of patients with Pompe disease, on the prevention and/or reduction of glycogen accumulation in the thyroid gland has not been studied.

All the patients with late-onset Pompe disease identified in this study were receiving ERT at the time of the study. Three of the five patients with hypothyroidism received a diagnosis of hypothyroidism prior to being diagnosed with Pompe disease and prior to starting ERT. In the presence of levothyroxine treatment, the effects of ERT on hypothyroidism would be uninterpretable. For patients with Pompe disease who are not receiving levothyroxine, but who have high-normal or slightly raised TSH, such longitudinal data capturing impact, if any, of ERT on thyroid functioning would be of great interest and could be designed into future studies.

This study has limitations. First, and most notably, the Pompe population study size was markedly small. This limitation, however, is not uncommon in studies of patients with rare diseases. Further expanded thyroid testing investigation on a larger sample from a national database in Pompe disease would be of interest. The authors did, in fact, request a query from a national Pompe disease database, specifically, the Genzyme-funded registry called the “Pompe Registry”, with the goal to survey a larger sample size. To date, the Pompe Registry is the largest Pompe disease patient registry. Unfortunately, the query was not able to be executed, as the Pompe Registry currently does not capture data on hypothyroidism in patients with Pompe disease.

Secondly, due to the retrospective nature of the study, primary data from the time of diagnosis was available in only three of the five hypothyroid subjects who had Pompe disease. *Anti*-thyroid antibody measurements were not available on any of the subjects. Thirdly, the diagnosis of hypothyroidism was defined by the treating physicians and more subtle age-specific abnormalities may have been missed. For example, it could be argued that subject #2 might have early, undiagnosed hypothyroidism, based on the available thyroid function tests and his age [6] (which would further raise the estimated prevalence in this Pompe disease population) [8]. Fourth, the UMMC clinical data repository query used only ICD9 code 244.9 (hypothyroid, not otherwise specified) which is limited by precise coding and which would not have included other more specific diagnoses related to hypothyroidism, some of which would have provided more valid comparisons than others. The large number of patient charts that were screened (i.e., 1.78 million records and over 56,000 records with a diagnosis of hypothyroidism), precluded feasibility of further review of the charts for accuracy of the diagnosis or ICD9 coding. For example, hypothyroidism due to Hashimoto thyroiditis, thyroidectomy or radioactive iodine each have different ICD9 codes. While Hashimoto thyroiditis would be a valid inclusion in the adult hypothyroid population compared with our Pompe disease population, post-treatment hypothyroidism would not. Still, the UMMC prevalence for hypothyroidism we report is consistent with literature reports, and the observed prevalence of hypothyroidism in our Pompe disease population far exceeds that reported in the literature.

This study suggests there may be a higher prevalence of hypothyroidism in patients with late-onset Pompe disease compared to the general adult population. In the primary care setting, the differential diagnosis for adult patients complaining of symptoms of muscle weakness, reduced endurance and fatigue commonly includes thyroid dysfunction. Consideration of more rare conditions, such as Pompe disease, typically does not occur early in the diagnostic process. Earlier consideration of Pompe disease is reasonable in these patients. In patients receiving treatment for hypothyroidism who have a persistently elevated CK, Pompe disease should be considered. This study sets precedent for further research aimed at better defining the impact of Pompe disease and ERT on thyroid function, and highlights the broader need for better understanding of the impact of different lysosomal diseases on thyroid function as well as other endocrine functions.

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