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Cardiac involvement in adults with Pompe disease

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Abstract. Soliman OII, van der Beek NAME, van Doorn PA, Vletter WB, Nemes A, Van Dalen BM, ten Cate FJ, van der Ploeg AT, Geleijnse ML (Erasmus University Medical Center, Rotterdam, The Netherlands). Cardiac involvement in adults with Pompe disease. *J Intern Med* 2008; **264**: 333–339.

Background. Glycogen storage disease type II or Pompe disease is a neuromuscular disorder caused by deficiency of lysosomal acid α- glucosidase. Classic infantile Pompe disease results in massive left ventricular (LV) hypertrophy and failure. Although Pompe disease is often included in the differential diagnosis of LV hypertrophy the true frequency of cardiac involvement in adults with Pompe disease is not known.

Methods. Forty-six consecutive adult patients (mean age 48 ± 12, 22 men) with Pompe disease were included. Each patient underwent a clinical examination, electrocardiography, and rest and low-dose dobutamine (in 20 patients) two-dimensional echocardiography including contrast and tissue Doppler imaging.

Results. All patients had limited exercise tolerance; a rollator walking aid was used in seven patients (15%), a wheelchair in 13 patients (28%), and assisted ventilation in 14 patients (30%). Prior to this study, one patient was known with permanent atrial fibrillation, His-bundle ablation and a VVI pacemaker and another patient was known with fluid retention. The first patient had increased LV end-diastolic diameter, impaired LV ejection fraction, low systolic mitral annular velocities and diastolic dysfunction grade II. The patient with fluid retention was wheelchair bound and dependent on 24-h assisted ventilation and showed right ventricular and LV hypertrophy (septum 16 mm, posterior wall 15 mm). LV hypertrophy was not seen in any of the other patients. One woman of advanced age had isolated low systolic mitral annular velocities. Mean global systolic LV function, including contractile reserve, was not decreased in patients with Pompe disease. Eight patients (17%) had mild diastolic dysfunction grade I, related to hypertension in four and advanced age in seven.

Conclusions. In adult patients with Pompe disease without objective signs of cardiac affection by 12-leads electrocardiography or physical examination, echocardiographic screening for LV hypertrophy seems not effective.

Keywords: cardiomyopathy, echocardiography, glycogen storage disease.

Introduction

Glycogen storage disease type II (GSD II), or Pompe disease, is an autosomal recessive disorder caused by inherited deficiency of α-1,4-glucosidase (acid maltase), a lysosomal enzyme that hydrolyses glycogen into glucose [1]. The disease has an incidence of approximately 1 : 40 000 births and affects various body tissues, especially muscle tissue [2, 3]. The genetic abnormality is in the GAA gene, traced to the long arm of chromosome 17 [2, 3]. Glycogen is present in excessive amounts in Pompe disease, both

within lysosomes and free in the cytoplasm [4]. Patients usually die in the first years of life from cardio-respiratory failure due to massive left ventricular (LV) hypertrophy [5]. A partial deficiency of α-glucosidase activity leads to milder, late-onset phenotypes Pompe disease [6, 7]. Adult patients with Pompe disease generally have a relatively slow disease progression and usually die because of respiratory failure [6, 7]. Still, glycogen storage diseases are often mentioned in the differential diagnosis of LV hypertrophy in adults [5]. The present study for the first time sought to assess in detail cardiac abnormalities with emphasize on LV dysfunction and hypertrophy in adult patients with Pompe disease.

Methods

Study population

In collaboration with our department of neurology, a standard program was initiated to prospectively investigate cardiac function with a 12-lead electrocardiogram and detailed echocardiography in a large (n = 46) cohort of adult patients with Pompe disease (first symptoms reported by the patients and diagnosis after the age of 18 years). The diagnosis Pompe disease was confirmed in all patients through mutation analysis (compound heterozygote with the common c.-32-13T>G mutation on one allele) and measurement of decreased acid a-glucosidase activity in leukocytes or fibroblasts. Mean age of the patients was 48 ± 12 years (range 25–71 years) and 22 patients (48%) were male. All patients gave informed consent before participating in the study and the institutional review board approved the study.

Clinical studies

In all patients respiratory function and exercise tolerance was semi-quantitatively estimated. Respiratory function was graded as 0 = normal, 1 = partial dependence on assisted ventilation, and 2 = 24-h dependence on assisted ventilation. Exercise tolerance was graded as 0 = normal, 1 = limited, 2 = dependence on a rollator walking aid, 3 = dependence on a wheelchair.

Two-dimensional echocardiography

Echocardiographic studies were performed with a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) by a single, experienced sonographer (WBV). The acquired data were digitally stored and subsequently analysed by two observers (MLG, OIIS) who were blinded for the clinical data. All echocardiographic measurements were averaged from three beats. From the second harmonic M-mode recordings the following data were acquired: left atrial dimension (normal value ≤40 mm), LV end-diastolic septal and posterior wall thickness, and LV end-diastolic dimension (normal value ≤56 mm). LV volume and septal thickness assessment was optimized with SonoVue contrast [8]. LV ejection fraction was calculated from LV volumes by the modified biplane Simpson rule in accordance with guidelines (normal value ≥50%) [9]. LV mass was calculated using the modified Devereux formula and indexed by body surface area (normal values in men: ≤150 g m^{-2}, in women ≤120 g m^{-2}) [10]. From the mitral-inflow pattern peak early (E) and late (A) filling velocities, E/A ratio, E-velocity deceleration time and duration of A-velocity were measured. Pulmonary vein systolic and diastolic flow and atrial reversal (velocity and duration) were also measured. Diastolic function was subsequently graded 1 to 4 according to an accepted protocol [11].

Tissue Doppler imaging

Tissue Doppler was applied end-expiratory in the pulsed-wave Doppler mode at the level of the inferoseptal and anterolateral side of the mitral annulus from an apical 4-chamber view. To acquire the highest wall tissue velocities, the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level. The tissue pulsed-wave Doppler velocity range was adjusted to obtain an appropriate scale. LV systolic (LV-S_m), and early diastolic (E_m) peak velocities were averaged from three samples. Subsequently, mean (calculated from the inferoseptal and anterolateral wall) S_m, mean E_m and the dimensionless parameter E/mean E_m were calculated.

Normal values for mean LV-S_m were calculated from 46 for age and gender matched healthy volunteers with normal left atrial and LV dimensions and LV function as described before [12]. The normal lower cut-off value for mean LV-S_m was 7.6 cm s^{-1}. The (volunteers and literature derived) normal higher cut-off value for E/E_m, indicating a most likely low end-diastolic LV pressure, was set to 9 [13, 14].

Low-dose dobutamine stress echocardiography

In the first 20 patients and in healthy volunteers (matched for age and gender) a low-dose dobutamine (10 μg kg^{-1} min^{-1}) contrast stress echocardiogram was performed according to standard recommendations [15] to assess increases in stroke volume and LV-S_m (contractile reserve).

Results

Clinical presentation

All patients had limited exercise tolerance, a rollator walking aid was used in seven patients (15%), and a wheelchair was used in 13 patients (28%). Assisted ventilation was used in 14 patients (30%), of whom one was 24-h dependent on assisted ventilation. Prior to this study, a 67-year-old male (patient no. 4) was known with permanent atrial fibrillation treated with His-bundle ablation and a VVI pacemaker. One 57-year-old male (no. 24) was known with fluid retention treated with furosemide and spironolacton.

Rhythm and conduction abnormalities

Apart from the previously mentioned patient no. 4 known with VVI pacing, conduction abnormalities were present in three other patients (7%). The previously mentioned patient no. 24 known with fluid retention had right bundle branch block with left anterior hemi-block, patient no. 21 (a 50-year-old female) had left bundle branch block, and patient no. 27 (a 45-year-old male) had isolated left anterior hemi-block. One patient (no. 23, a 35-year-old female) without palpitations showed an atrial rhythm (positive P-waves in leads I and II, flat P-wave in lead aVF) with a short PR-interval of 114 ms without evidence of a δ-wave.

Left atrial and LV dimensions

The 67-year-old male (patient no. 4) known with permanent atrial fibrillation, His-bundle ablation and a VVI pacemaker had an increased LV end-diastolic diameter. The 57-year-old wheelchair bound male (patient no. 24) dependent on 24-h assisted ventilation and known with fluid retention had right ventricular and LV hypertrophy (septum 16 mm, posterior wall 15 mm) but due to relatively small LV size, LV mass was still within the normal range. Minor nonspecific septal sparkling was present in a 68-year-old woman (patient no. 35) with normal left atrial and LV dimensions and normal LV mass.

LV systolic function

Overt systolic LV dysfunction, evidenced by a 48% LV ejection fraction and low systolic TDI values, was present in the previously mentioned 67-year-old male (patient no. 4) known with permanent atrial fibrillation, His-bundle ablation and a VVI pacemaker. The previously described 68-year-old woman (patient no. 35) with minor aspecific septal sparkling, normal left atrial and LV dimensions and normal LV mass had isolated low systolic mitral annular velocities. All other patients had normal parameters of LV systolic function (see Table 1). Stroke volume increase during low-dose dobutamine in Pompe patients and healthy volunteers was not different (95 ± 25 to 109 ± 32 mL, 18% increase vs. 81 ± 19 to 96 ± 27 mL, 19% increase). Also, the increase in mean LV-S_m was not different in Pompe patients and healthy volunteers (9.7 ± 1.2 to 12.7 ± 1.9 cm s^{-1}, 31% increase vs. 9.1 ± 1.4 to 12.4 ± 2.2 cm s^{-1}, 36% increase).

Diastolic function

Nine patients had mild diastolic dysfunction. Grade I dysfunction without evidence for increased LV filling pressures was present in eight patients (nos 8, 18, 19, 34, 35, 42, 44 and 46) and grade II dysfunction was present in the previously mentioned 67-year-old male

Table 1 Demographic and clinical characteristics of the patients with Pompe disease

Pt	Age	Sex	DM/HT	Symptom onset age	Exercise tolerance[a]	Ventilation[b]	LA size (mm)	LV-EDD (mm)	LV mass index (g m^{-2})	LV-EF (%)	LV-Sm (cm s^{-1})	Diastolic dysfunction grade	E/E_m
1	25	F	−/−	18	**1**	0	32	38	69	60	8.5		5.6
2	26	F	−/−	18	**2**	0	29	41	58	64	8.1		7.8
3	37	M	−/−	18	**1**	**1**	39	46	64	53	11.0		7.0
4	67	M	−/−	20	**2**	0	38	**58**	134	**48**	**5.1**	**II**	13.3
5	37	F	−/−	22	**1**	**1**	30	49	70	52	8.1		8.6
6	30	M	−/−	23	**1**	0	33	49	85	84	12.9		6.6
7	38	F	−/−	23	**3**	0	30	46	60	82	10.7		3.9
8	60	F	−/−	23	**3**	0	28	40	64	66	8.3	**I**	8.7
9	30	M	−/−	23	**1**	0	40	55	81	54	11.0		3.6
10	39	F	−/−	24	**1**	0	34	43	63	52	9.9		7.6
11	34	F	−/−	24	**1**	0	35	51	83	68	8.7		7.1
12	36	F	+/+	26	**1**	**1**	33	49	77	68	8.3		6.5
13	47	M	−/+	26	**2**	**1**	31	50	97	60	9.4		4.4
14	50	F	−/−	28	**3**	0	34	43	72	70	9.1		7.9
15	49	M	−/+	29	**1**	0	32	55	87	69	9.7		4.0
16	63	M	−/+	29	**3**	**1**	31	52	78	74	10.1		6.2
17	37	M	−/−	29	**1**	0	34	53	91	69	10.0		5.7
18	41	M	−/+	30	**1**	**1**	28	52	68	70	9.5	**I**	5.4
19	67	M	−/−	30	**3**	**1**	32	36	47	62	10.8	**I**	5.7
20	65	M	−/−	31	**3**	0	39	51	80	74	9.1		5.6
21	50	F	−/−	31	**3**	0	29	46	83	69	10.6		4.0
22	37	M	−/−	32	**1**	0	26	53	102	64	8.6		5.1
23	34	F	−/−	33	**1**	0	28	45	95	57	9.9		4.2
24	57	M	−/−	33	**3**	**2**	32	39	122	67	NA	NA	NA
25	38	M	−/−	33	**1**	0	30	47	89	59	10.2		6.4
26	43	F	+/−	35	**3**	0	28	50	84	68	10.6		6.1
27	45	M	−/−	35	**1**	0	35	46	82	69	11.2		4.6
28	40	F	−/−	36	**1**	0	30	51	82	58	8.3		6.6
29	51	F	−/+	36	**3**	0	34	44	70	61	9.2		7.4
30	41	M	−/−	36	**2**	0	30	41	66	64	10.8		6.5
31	42	F	−/−	36	**1**	0	31	51	75	53	7.6		6.1
32	41	F	−/−	37	**1**	0	35	42	72	63	11.7		4.7
33	53	M	−/−	38	**2**	0	40	48	88	52	8.6		8.0
34	55	M	−/+	39	**1**	**1**	31	50	90	69	8.3	**I**	3.7
35	68	F	−/−	40	**3**	**1**	28	46	71	78	**6.3**	**I**	5.7
36	48	F	−/+	40	**1**	0	32	41	68	74	10.4		4.9
37	46	M	−/−	40	**1**	0	30	52	64	69	8.1		6.3
38	57	F	−/−	41	**2**	**1**	28	53	92	71	9.0		5.5
39	50	F	−/−	43	**1**	0	28	46	78	68	8.4		7.1
40	47	F	−/−	43	**1**	0	30	43	78	58	8.2		5.0

Table 1 (*Continued*)

Pt	Age	Sex	DM/HT	Symptom onset age	Exercise tolerance[a]	Ventilation[b]	LA size (mm)	LV-EDD (mm)	LV mass index (g m^{-2})	LV-EF (%)	LV-Sm (cm s^{-1})	Diastolic dysfunction grade	E/E$_m$
41	52	F	−/−	44	**2**	0	33	51	72	80	9.5		7.8
42	61	M	−/+	44	**3**	**1**	37	45	71	71	15.5	**I**	6.8
43	52	M	−/+	46	**1**	0	40	50	89	62	9.8		6.4
44	59	M	−/−	47	**1**	**1**	38	43	51	51	10.4	**I**	5.8
45	55	F	−/−	49	**1**	**1**	31	40	64	80	9.3		4.8
46	71	F	−/+	62	**3**	0	28	45	69	69	10.1	**I**	4.1

DM, diabetes mellitus; E, early passive mitral inflow; E$_m$, early mitral annular tissue velocity; LA, Left atrium; LV-EDD, LV end-diastolic diameter; LV-EF, LV ejection fraction; LV-Sm, LV systolic velocities averaged from septal and lateral mitral annulus; HT, Hypertension.
[a]Exercise tolerance: 1 = limited, 2 = (rollator) walking aid, 3 = wheelchair.
[b]Assisted ventilation: 0 = none, 1 = <24 h respirator, 2 = 24 h assisted ventilation).
Values in bold are abnormalities.

(patient no. 4) with permanent atrial fibrillation, His-bundle ablation and a VVI pacemaker. Unfortunately, tissue Doppler measurements could not be obtained reliably due to angulation problems in the previously described patient no. 24 with right ventricular and LV hypertrophy.

Discussion

This is the first study in which cardiac involvement in a large, nonselected series of adult patients with Pompe disease was studied in detail. The incidence of atrio-ventricular conduction abnormalities and LV hypertrophy was markedly lower than that reported in the literature on classic infantile Pompe disease [16]. In our series of 46 adult patients with Pompe disease only one wheelchair-bound patient dependent on assisted ventilation and known with fluid retention showed right ventricular and LV hypertrophy and one other patient had a short PR-interval.

Electrocardiographic abnormalities

A short PR interval without evidence of a δ-wave in the presence of an atrial rhythm was seen in one patient without palpitations. In previous reports in classic infantile patients, high incidences of pre-excitation, defined as a short PR-interval, were reported [17, 18]. Also, Wolf-Parkinson-White syndrome has been reported to occur in Pompe disease [19]. The presumed electrophysiological basis of accelerated atrio-ventricular conduction in Pompe disease may be related to the insulator effect of glycogen in atrio-ventricular conduction tissue [20]. Even when we consider our patient to really have abnormal atrio-ventricular conduction (this may also be physiological in the presence of a low atrial rhythm), a coincidental occurrence of pre-excitation and Pompe disease in this single patient cannot be ruled out since the prevalence of pre-excitation in the general population may be as high as 3% [21]. In addition, the prevalence of conduction abnormalities in the bundle branches found in our study (7%) is not higher than that amongst the general population [22, 23].

Echocardiographic abnormalities

It is well known that in neonates with Pompe disease glycogen accumulation can result in massive LV hypertrophy [5]. In our study, only a 57-year-old wheelchair bound male dependent on assisted ventilation and known with fluid retention had right ventricular and LV hypertrophy. It is important to realize that LV septal thickness assessment in our study was optimized with SonoVue contrast [8] to reliably exclude LV hypertrophy. Mean global systolic LV function, including contractile reserve, was not decreased in patients with Pompe disease. Minor cardiac abnormalities (isolated low systolic mitral annular velocities or mild LV diastolic dysfunction) were

present in a few patients. The patient with isolated low systolic mitral annular velocity (no. 35) was of advanced age. All patients with mild diastolic dysfunction grade I had a history of hypertension (nos 18, 34, 42, 46) or had advanced age (nos 8, 19, 35, 42, 44, 46), conditions well known to be related to lower systolic mitral annular velocities and mild diastolic dysfunction [11, 24, 25]. Despite the inclusion of Pompe disease in the differential diagnosis of LV hypertrophy in cardiac textbooks our study results seem not to justify this for adults with Pompe disease. Recently, Arad *et al.* found in none of the 75 adult patients with unexplained LV hypertrophy evidence for Pompe disease [5]. Since in our study even in patients with severe skeletal or respiratory muscle affection none of the aforementioned echocardiographic methods found any alterations suggesting LV hypertrophy it seems certainly not indicated to screen patients with normal skeletal muscle function and LV hypertrophy for Pompe disease.

Genetic basis of Pompe

Pompe disease is an autosomal recessive disorder resulting from abnormalities in the GAA gene, traced to the long arm of chromosome 17 [3, 26]. All our patients had the c.-32-13T>G mutation on one allele which is the most frequent mutation seen in patients with Pompe [27]. In infants with the classic infantile phenotype, severe myocardial hypertrophy obliterates the LV lumen and causes LV outflow obstruction in virtually all patients, resulting in fatal cardiac failure [28, 29]. The impressive difference in the prevalence and severity of cardiac involvement in infants compared to adults seen in this study is most likely due to the higher amount of residual α-glucosidase activity in adults [30]. A low level of enzyme activity seems sufficient to prevent intra-lysosomal accumulation of glycogen in cardiomyocytes. In addition, there are differences in storage capacity and metabolism of heart and skeletal muscle [31].

Conclusions

Apart from abnormalities in a patient known with permanent atrial fibrillation, His-bundle ablation and a VVI pacemaker and a single patient with cardiac hypertrophy, none of our adult patients with Pompe disease showed major cardiac abnormalities. All minor cardiac abnormalities could be explained by a history of longstanding hypertension and/or advanced age. Because, in adult patients with Pompe disease without objective signs of cardiac affection by 12-leads electrocardiography or physical examination, none of the aforementioned echocardiographic methods found any alterations suggesting LV hypertrophy or overt LV dysfunction, echocardiographic screening seems not effective.

Conflict of interest

None.

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