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Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease

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ABSTRACT: The objective of the present study was to prospectively evaluate relationships linking age, respiratory function and locomotor function in 29 outpatients with late-onset Pompe's disease and to retrospectively determine clinical outcomes.

Using univariate regression analysis, vital capacity (VC) was weakly, but significantly, correlated to shoulder motility, Walton score and lower-limb Modified Medical Research Council score. Six patients were able to walk without a walking aid and with only the help of a handrail on the stairs (Walton score=3), although VC was <50%. No parameters were significantly correlated with age.

As assessed retrospectively, VC and locomotion deteriorated over time in most patients. In contrast, among the 16 patients started on invasive or noninvasive ventilation with VC monitoring, eight had a VC increase at the first measurement time-point.

The absence of correlation with age and the presence, in some patients, of severe respiratory insufficiency without severe limb girdle muscle weakness indicate that respiratory function should be monitored independently from the degree of peripheral muscle weakness. Mechanical ventilation and tracheostomy may improve vital capacity and should, therefore, be taken into account when evaluating treatments for the adult form of Pompe's disease.

KEYWORDS: Acid maltase deficiency, α-glucosidase, glycogen storage disease type II, neuromuscular disease, Pompe's disease, pulmonary function

Pompe's disease, also named acid maltase deficiency or glycogen storage disease type II, is an autosomal recessive disorder characterised by a deficiency in the lysosomal enzyme acid α-glucosidase (GAA). The spectrum of this disease is wide and varies from a rapidly progressive infantile disease with cardiorespiratory insufficiency, which is usually fatal before 1 yr of age [1], to a slowly progressive adult-onset disease with muscle weakness, respiratory insufficiency [1, 2] and sleep-disordered breathing [3]. Adults typically present with progressive myopathy that may resemble limb-girdle muscular dystrophy [4]. However, both the presenting symptoms and the clinical outcomes in adults seem to vary widely. Although respiratory muscle involvement is rarely inaugural [5, 6], it may occur early in the course of the disease and may cause death. These characteristics, and the likelihood that new treatments recently tested in infantile and juvenile Pompe's disease [7–10] will require evaluation in adult-onset disease, indicate a need for investigations into the relationships between respiratory muscle weakness and weakness in other muscles. This will clarify outcomes in adults and assess the effects of both noninvasive mechanical ventilation (MV) and tracheostomy.

The objectives of the present study were to evaluate relationships linking age, respiratory function and locomotor function, and to assess clinical outcomes in the adult form of Pompe's disease.

METHODS

In total, 29 patients with late-onset Pompe's disease were investigated prospectively as part of routine follow-up. Patients who required MV or respiratory function evaluation were studied at the Raymond Poincaré Teaching Hospital (Garches, France) and the other patients at the Myology Institute, Pitié-Salpêtrière Teaching Hospital (Paris, France). The diagnosis was confirmed by assessment of low GAA activity in leukocytes in all patients [11] and by identification of the gene mutations in 11 patients [12]. Physical examinations were carried out by a neurologist (B. Eymard or P. Laforet) or physical therapist (N. Pellegrini).

For editorial comments see page 984.

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Locomotor function

The evaluation consisted of an interview regarding occupational activities, ability to swallow without difficulty, ability to control urination and presence of chronic pain (*e.g.* in the back, neck or muscles). Functional activity was assessed using the Gardner, Medwin and Walton score (where 0=normal and 10=bed bound) [13]. Muscle power of the quadriceps femoris, hip flexors and gluteus medius on both sides of the body was graded using the Modified Medical Research Council (MMRC) scale, which has been used in muscle diseases, such as Duchenne muscular dystrophy [14]. The MMRC scale has six grades (0 to 5) followed by + or − for some values (*e.g.* 1+, 2-, 2+, 3-, 3+). The current authors transformed + and − to +0.33 and -0.33, respectively. For each muscle, the mean value for the right and left limbs was used. Therefore, the total MMRC score could range from 0 to 15. The range of active shoulder abduction with the elbow extended was measured in degrees (0–180°), and the mean of the right and left side was used. Care was taken to check that limitation was not due to pain or to skeletal conditions such as frozen shoulder. Therefore, shoulder abduction evaluated the synergic contraction of the deltoid, supraspinatus, serratus anterior and trapezius.

Lung and respiratory muscle function

Sniff nasal pressure (P_{sn}) and maximal inspiratory pressure (P_{Imax}) were both measured from the functional residual capacity (FRC) in a standard manner. As previously described, P_{Imax} is an isometric manoeuvre and P_{sn} a quasi-isometric manoeuvre [15, 16]. These variables were obtained for the patients evaluated at the Raymond Poincaré Teaching Hospital. P_{sn} was measured during 10 maximal sniffs [17]. P_{Imax} was measured using a flanged mouthpiece with the manoeuvres repeated at least three times, or until two identical readings were obtained [18]. All signals were measured using a differential pressure transducer (Validyne, Northridge, CA, USA), amplified by a carrier amplifier (Validyne) and passed *via* an analogue-digital board to a computer running Acqknowledge software (Biopac System, Santa Barbara, CA, USA). Patients received strong verbal encouragement with visual feedback, as in previous studies [19]. The best value of the two measurement methods was taken as the P_{Imax}.

For the patients who accepted, transdiaphragmatic pressure (P_{di}) was obtained by measuring the differential between gastric pressure and oesophageal pressure using a catheter-mounted pressure transducer system (Gaeltec, Isle of Skye, UK). The catheter was inserted through the nose, following administration of local anaesthesia, to the nasal mucosa. The position of the catheter was assessed by asking the subject to perform sharp sniff manoeuvres, whilst observing signal deflection. The oesophageal and gastric transducers were advanced into the stomach, *i.e.* until a positive deflection occurred while one of the operators applied gentle pressure to the patient's stomach, and the catheter was then withdrawn until a drink of water induced a sharp rise in the proximal transducer pressure (resulting from muscular contraction of the oesophagus) without any concomitant modification of the distal transducer pressure. This indicated that the proximal transducer was in the oesophagus and the distal transducer in the stomach. An occlusion test was carried out to assess the validity of the oesophageal pressure measurement [20]. Following this, cervical magnetic phrenic nerve stimulation, *via* a 90 mm circular coil powered by a Magstim stimulator (Magstim Company, Whitland, UK), was used to determine the twitch transdiaphragmatic pressure (TwP_{di}) [21]. This is a sensitive and reliable nonvolitional technique for assessing diaphragm function [21]. All the magnetic stimulations were applied at FRC, determined by the end-expiratory oesophageal pressure level [19, 22]. Mean TwP_{di} was calculated from at least five phrenic nerve stimulations at maximal power output. P_{di} pressure change was also measured during sniff manoeuvres and maximal inspiratory manoeuvres were performed as described above to obtain maximal transdiaphragmatic pressure (P_{dimax}). Spirometry and lung volume measurements were performed according to standard guidelines at both hospitals and reported as per cent predicted [23].

Retrospective assessment of muscle weakness progression

The medical records of the study patients were reviewed in detail to obtain information on outcomes reflecting the progression of muscle weakness.

Statistical analysis

Data were expressed as mean±SD. The differences between patients who did and did not use MV were compared using an unpaired t-test. Fisher's exact test was used to compare prevalence rates in the two groups. In addition, using the values at the time of the study for least-square simple linear regression analysis, the present authors looked for correlations between age and other data, as well as between vital capacity (VC) and inspiratory muscle and locomotor data. A full-model, stepwise, multiple linear regression analysis was then performed to determine the influence of each variable. The level of significance was set at 5%.

RESULTS

Prospective evaluation

The clinical characteristics of the patients are reported in table 1. Mean age was 55±11 yrs. In total, 29 patients were followed at both hospitals, eight only at the Myology Institute and two only at the Raymond Poincaré Teaching Hospital. GAA activity was deficient in leukocytes in all patients. Genetic testing showed mutations in 11 patients, of whom six had mutations in both alleles and five in a single allele [12]. Age at symptom onset was 16–70 yrs (41±11). Of the patients, five were retired, five worked full time, three worked part time and 16 were on sick leave or disability allowance.

Pain in the back, neck, shoulders and/or limbs was reported by 22 patients. Only seven patients were free of pain. Shoulder pain did not affect range of motion. Intermittent loss of bladder control was reported by seven patients and difficulty swallowing by five patients.

Of the study patients, 16 accepted to undergo P_{di} measurement during volitional manoeuvres (P_{Imax} measurement) and nonvolitional manoeuvres (cervical magnetic stimulation; table 1). Significant correlations were found between VC and P_{Imax}, P_{Imax} and P_{dimax}, and P_{dimax} and TwP_{di} (fig. 1).

Among the 16 patients using MV, five had a tracheostomy (table 2). Age at MV initiation was 50±12 yrs (range 20–70 yrs).

TABLE 1 Clinical characteristics of the 29 study patients

Patient	Age yrs	Sex	MV	VC %	P_{Imax} cmH_2O	P_{dimax} cmH_2O	TwP_{di} cmH_2O	Lower-limb MMRC scale	Shoulder abduction degrees	Walton score
1	46	M	Y	32	14	NA	NA	11.99	180	3
2	59	F	Y	37	NA	NA	NA	5.66	0	7
3	71	M	Y	39	13	0	0	9.32	60	3
4	58	M	Y	20	8	0	0	NA	NA	6
5	52	M	Y	29	NA	NA	NA	8.99	65	3
6	47	M	Y	36	18	21	3	6.49	110	3
7	58	F	Y	29	22	NA	NA	6.50	145	6
8	55	M	Y	46	32	8	2	9.16	180	4
9	74	F	Y	64	32	4	<1	8.16	90	6
10	60	F	Y	33	19	10	2	4.00	30	8
11	60	M	Y	54	20	0	0	9.32	145	3
12	71	F	Y	43	18	NA	NA	8.17	155	3
13	42	M	Y	46	20	1	0	8.00	100	3
14	27	F	Y	13	8	12	2	5.32	65	8
15	57	M	Y	60	43	38	7	9.50	165	3
16	57	F	Y	47	18	NA	NA	6.66	NA	7
17	38	F	N	57	36	35	9	8.16	180	3
18	53	F	N	86	69	90	25	8.34	180	3
19	55	F	N	115	NA	NA	NA	11.00	180	3
20	37	M	N	45	50	40	7	8.33	100	3
21	58	F	N	64	NA	NA	NA	8.99	180	4
22	74	F	N	58	31	21	3	10.16	180	3
23	50	F	N	101	NA	NA	NA	9.83	180	3
24	41	F	N	81	NA	NA	NA	10.66	180	3
25	62	F	N	96	NA	NA	NA	8.33	110	3
26	60	F	N	69	NA	NA	NA	NA	180	3
27	67	F	N	72	NA	NA	NA	9.33	100	3
28	47	M	N	95	47	45	8	NA	140	3
29	51	F	N	87	61	61	25	5.55	90	4

M: male; F: female; Y: yes; N: no; MV: mechanical ventilation; VC: vital capacity; P_{Imax}: maximal inspiratory pressure; P_{dimax}: maximal transdiaphragmatic pressure; TwP_{di}: twitch transdiaphragmatic pressure; MMRC: Modified Medical Research Council; NA: not available.

MV was initiated during an episode of acute respiratory failure in five patients (patients 1, 3, 5, 10, and 12, respectively), including two patients who underwent a tracheostomy during the same episode (patients 3 and 5). The remaining 11 patients received noninvasive MV and met international criteria for this modality [24]. Of these 11 patients, nine had diurnal hypercapnia >5.9 kPa (45 mmHg) and the remaining two patients had nocturnal oxyhaemoglobin desaturation with morning headaches (patients 4 and 7).

Five patients underwent overnight polysomnography before and after MV initiation (patients 5, 8, 10, 15 and 16, respectively). Prior to MV initiation, the apnoea–hypopnoea index was 18, 18, 8, 28, and 7, respectively, per hour of sleep and percentage of total sleep time spent with arterial oxygen saturation (S_{a,O_2}) <90% was 5, 28, 1, 21, and 4, respectively. When polysomnography was repeated in the same patients after MV initiation, the apnoea–hypopnoea index values were 0, 5, 5, 1, and 0, respectively, and the percentage of total sleep time with S_{a,O_2} <90% were 3, 21, 3, 0, and 0, respectively.

Tracheostomy was performed in two patients who failed to respond adequately to noninvasive MV (patients 4 and 14) and in one patient (patient 1) after a stroke responsible for impaired swallowing. MV modes and settings are reported in table 2. Most of the patients were ventilated with an assist-control volumetric mode and a back-up rate set two to three breaths below the awake spontaneous breathing rate, according to consensus conference guidelines [25].

When patients who did and did not use MV were compared, no difference in age was found (table 3). VC was significantly different between the two groups, as expected, but in addition differences were noted for locomotor function (table 2). Furthermore, in the univariate regression analysis, VC was significantly correlated with the Walton score, lower-limb MMRC score and shoulder mobility (table 4). The relationship between VC and the Walton score is shown in figure 2. However, it should be emphasised that six patients were able to walk without a walking aid and using only the handrail on the stairs (Walton score=3), although VC was <50% (table 4; fig. 2). No parameters were significantly correlated with age

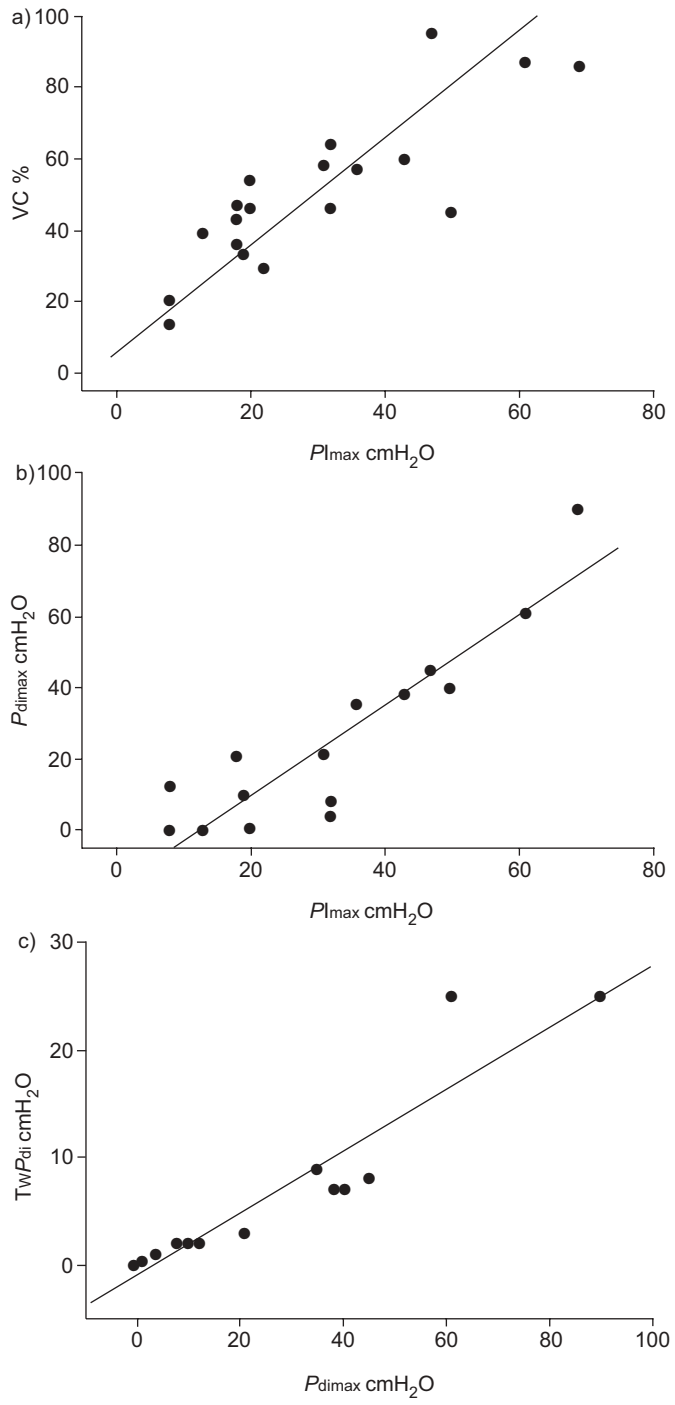

FIGURE 1. Correlations linking a) vital capacity (VC) to maximal inspiratory pressure (P_{Imax}; n=19, R^2=0.70, p<0.0001), b) P_{Imax} to the change in maximal transdiaphragmatic pressure (P_{dimax}; n=16, R^2=0.82, p<0.0001), and c) P_{dimax} to twitch transdiaphragmatic pressure ($Tw P_{di}$; n=16, R^2=0.88, p<0.0001). The straight lines represent the regression lines.

(lower-limb MMRC scale score, p=0.61; shoulder mobility, p=0.91; Walton score, p=0.92; VC, p=0.60; and P_{Imax}, p=0.96). In the stepwise multiple regression model, including the parameters significantly associated with VC in the univariate analysis, only the Walton score was independently correlated with VC (R^2=0.198; p=0.026).

Retrospective assessment of muscle weakness progression

Results of the retrospective VC assessment are shown in figure 3. Before MV, VC decreased gradually in most patients (fig. 3). In contrast, in the 16 patients started on invasive or noninvasive ventilation and subsequently monitored for VC changes, eight had an increase in VC at the first measurement time-point. None of these eight patients exhibited improvements in the Walton score or increases in body mass index. The first measurement after MV was performed during the first hospital admission following MV initiation, which occurred after 3–13 months. Among the eight patients whose VC improved, six underwent P_{Imax} measurement at MV initiation (patients 2, 8, 10, 11, 12 and 13, respectively) and at later time-points (nonpresented data). In four of these six patients no P_{Imax} increase was found (patients 10, 11, 12 and 13, respectively). The VC improvement was >5% of the predicted VC value in four patients (patients 3, 5, 10 and 12, respectively), who were among the five patients in whom MV was initiated because of acute respiratory failure. The Walton score is shown in figure 4. Although compliance with the follow-up program was worse before rather than after MV, the data do not suggest that starting MV may have abruptly worsened or subsequently improved the parameters reflecting locomotor function.

DISCUSSION

The present study showed a weak relationship between respiratory function and locomotor function in adults with late-onset Pompe's disease. Disease severity was not related to age. Retrospective data indicated a gradual decline in respiratory and locomotor function over time, as previously described by WOKKE *et al.* [26]. Interestingly, noninvasive MV initiation or tracheostomy did not seem to be associated with an abrupt deterioration in respiratory muscle function, in contradiction with the results of a review on the effects of MV [27]. However, several patients experienced a short-lived improvement in VC after MV initiation or tracheostomy.

Before discussing the implications of these findings, several methodological issues will be addressed. First, it could be argued that the youngest patient had juvenile onset (as symptoms first occurred at 15 yrs of age) and that this may have affected the results regarding correlations with age. Secondly, although the present study was mainly prospective, some data were missing and the time-course data were retrospective. Notwithstanding, the current study is one of the largest late-onset Pompe's disease series reported to date, and follow-up was ⩾5 yrs in 19 patients. Thirdly, for logistic reasons, P_{Imax} and diaphragm muscle performances were only measured in patients with severe disease. Given the shape of the normal respiratory system pressure–volume curve [28], a P_{Imax} decrease may ensure detection of respiratory muscle weakness before the occurrence of a decrease in VC. However, patients with chronic respiratory muscle weakness display a greater than expected decrease in VC related to concomitant decreases in lung and chest-wall compliance [28]. Fourthly, the Walton score is not continuous and logistic regression may, therefore, be better than least-square simple linear regression for testing the relationship between Walton score values and other variables. Nevertheless, when simple logistic regression

TABLE 2 Mechanical ventilation (MV) modes and settings

Patient	Tracheostomy	Time on ventilator per day h	Mode of MV	Delivered pressure cmH_2O	Delivered volume mL	Back-up rate breaths·min^{-1}
1	Y	9	ACV		700	16
2	N	9	ACV		650	17
3	Y	8	ACV		600	20
4	Y	10	ACV		500	18
5	Y	10	ACV		750	17
6	N	9	PSV	14		16
7	N	12	PSV	15		14
8	N	8	ACV		850	16
9	N	10	PSV	14		15
10	N	8	ACV		750	18
11	N	8	PSV	14		11
12	N	12	ACV		600	20
13	N	11	ACV		700	14
14	Y	24	ACV		520	15
15	N	8	PSV	15		12
16	N	6	ACV		600	15

Y: yes; N: no; ACV: assist-control ventilation; PSV: pressure-support ventilation.

was used to compare VC and Walton score values, the findings were unchanged (p=0.0174).

Respiratory failure has been found in about one third of patients with late-onset Pompe's disease [2, 5, 6]. In a recent questionnaire study in 54 patients of the Dutch Neuromuscular Diseases Association, registered has having late-onset Pompe's disease, HAGEMANS *et al.* [29] found that 20 patients used ventilatory assistance, having started at a mean age of 49 yrs, and that 23 patients used a wheelchair, starting at a mean age of 46 yrs. Fifteen patients used both ventilatory assistance and a wheelchair. Among them, three patients started both assistance modalities during the same year, six needed a wheelchair first and six needed assisted ventilation first. The present study corroborates these results and is the first to show a correlation between respiratory parameters and locomotor function. However, this correlation was weak. For example, patient 1 was able to walk and had normal shoulder mobility, but had a tracheostomy. Both the weak relationship between respiratory function and locomotor function and the absence of correlations between age and functional parameters indicates a need for routine respiratory function testing in adults before the development of respiratory failure, regardless of patient age or locomotor function.

Locomotor function was more severely impaired in the patients with rather than without MV, although age was similar in the two groups. Two hypotheses can be put forward to explain this finding. First, both respiratory function and locomotor function may reflect muscle weakness, as suggested by HAGEMANS *et al.* [29]. This hypothesis is consistent with the weak correlation between VC and locomotor function parameters. Secondly, MV may adversely affect locomotor function. However, although locomotor function was monitored more closely after than before MV, the data in figure 4 do not

TABLE 3 Characteristics of the patient groups with and without mechanical ventilation (MV)

	Patients with MV	Patients without MV	p-value
Subjects	16	13	
Age yrs	55.8±11.6	53.4±11.1	0.5788
VC %	39.2±13.7	78.9±20.2	<0.0001
Walton score	4.8±2.0	3.1±0.4	0.0092
Lower-limb MMRC scale	7.8±2.0	8.9±1.5	0.1271
Shoulder abduction degrees	106±57	157±38	0.0226
Employed in paid job	2/16	6/13	0.09
Pain	12/16	9/12	1.0

Data are presented as n or mean±SD, unless otherwise stated. VC: vital capacity; MMRC: Modified Medical Research Council.

TABLE 4 Univariate regression analysis of vital capacity % of the predicted value on other variables

	Coefficient	R^2	p-value
Age yrs	0.230	0.010	0.6080
Walton score	-0.032	0.241	0.0068
Lower-limb MMRC scale	0.038	0.220	0.0104
Shoulder abduction degrees	1.03	0.224	0.0096

MMRC: Modified Medical Research Council.

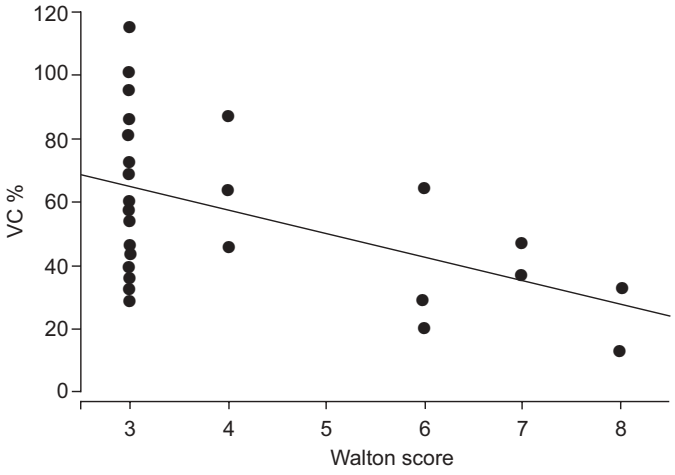

FIGURE 2. Negative correlation between vital capacity (VC) and the Walton score. The straight line represents the regression line (see also table 2).

suggest that MV initiation or tracheostomy may have caused an abrupt worsening (or improvement) in locomotor function. Thus, the first hypothesis is the most likely.

The current authors obtained information on the time-course of the muscle weakness in adults with late-onset Pompe's disease. This point is now of considerable interest, given that enzyme replacement therapy with recombinant human acid α-glucosidase has been tested in infantile and juvenile forms and will be evaluated in adults in the very near future [7–10]. Therefore, it is important to obtain data on the natural history of late-onset Pompe's disease. Interestingly, MV initiation with or without tracheostomy was found to be associated with a brief VC improvement in some patients, particularly in patients who required MV initiation due to acute respiratory failure. This is in keeping with a previous case report from the current authors' group [30]. Thus, MV may have beneficial effects, probably *via* an increase in lung compliance related to a decrease in diffuse microatelectasis. MV initiation and tracheostomy must be taken into account in future evaluations of enzyme replacement therapy in late-onset Pompe's disease. Another hypothesis is that acute respiratory failure may temporarily affect respiratory muscle performance. Unfortunately, the first measurement after MV was performed during the next hospital admission, which occurred after 3–13 months. Furthermore, among the four patients who experienced a VC improvement >5% of the predicted VC, only two underwent $P\mathrm{I}_{max}$ measurement. No concomitant $P\mathrm{I}_{max}$ improvement was found. Nevertheless, it has been reported that a simple acute upper respiratory tract infection in patients with neuromuscular disease can cause a VC decrease related to a reduction in respiratory muscle strength, followed by a prompt improvement in VC in parallel with resolution of the infection [31]. Thus, a reduction in inspiratory muscle strength during acute respiratory failure cannot be ruled out in the current population.

In conclusion, the present study showed a gradual decline in respiratory and locomotor function over time, as well as a weak correlation between respiratory and locomotor function in adults with late-onset Pompe's disease. Respiratory and locomotor functions were not correlated with age. Age at onset

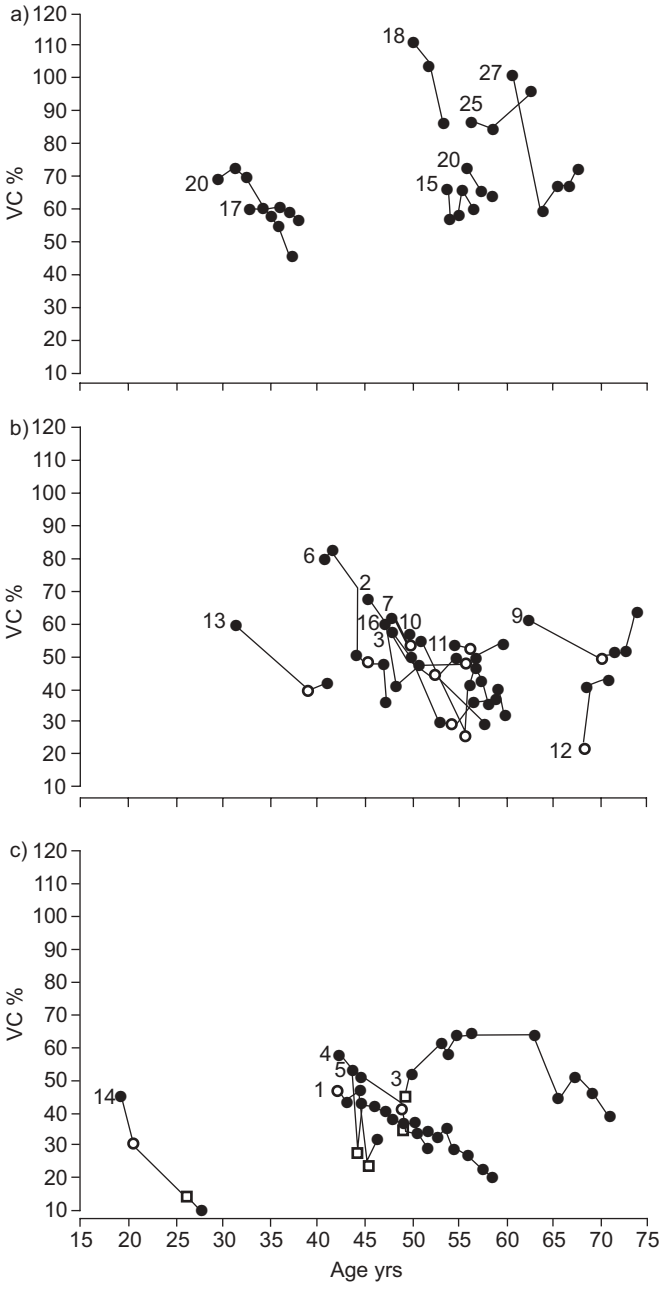

FIGURE 3. Individual results for vital capacity (VC) changes over time before and after mechanical ventilation initiation. Each patient is individualised by its number (see table 1). a) Patients for whom mechanical ventilation and tracheostomy has not been indicated. b) Patients for whom noninvasive ventilation has been indicated, but not tracheostomy. c) Patients for whom tracheostomy has been indicated. ○: indicate the beginning of noninvasive ventilation; □: indicate the age of tracheostomy.

of respiratory and limb muscle weakness varied across patients. The absence of correlations with age and the weak correlation between respiratory function and locomotor function indicates a need for routine serial evaluations of both functions in patients. In addition, because mechanical ventilation and tracheostomy may improve vital capacity, they should be taken into account in future evaluations of enzyme therapy with recombinant human acid α-glucosidase.

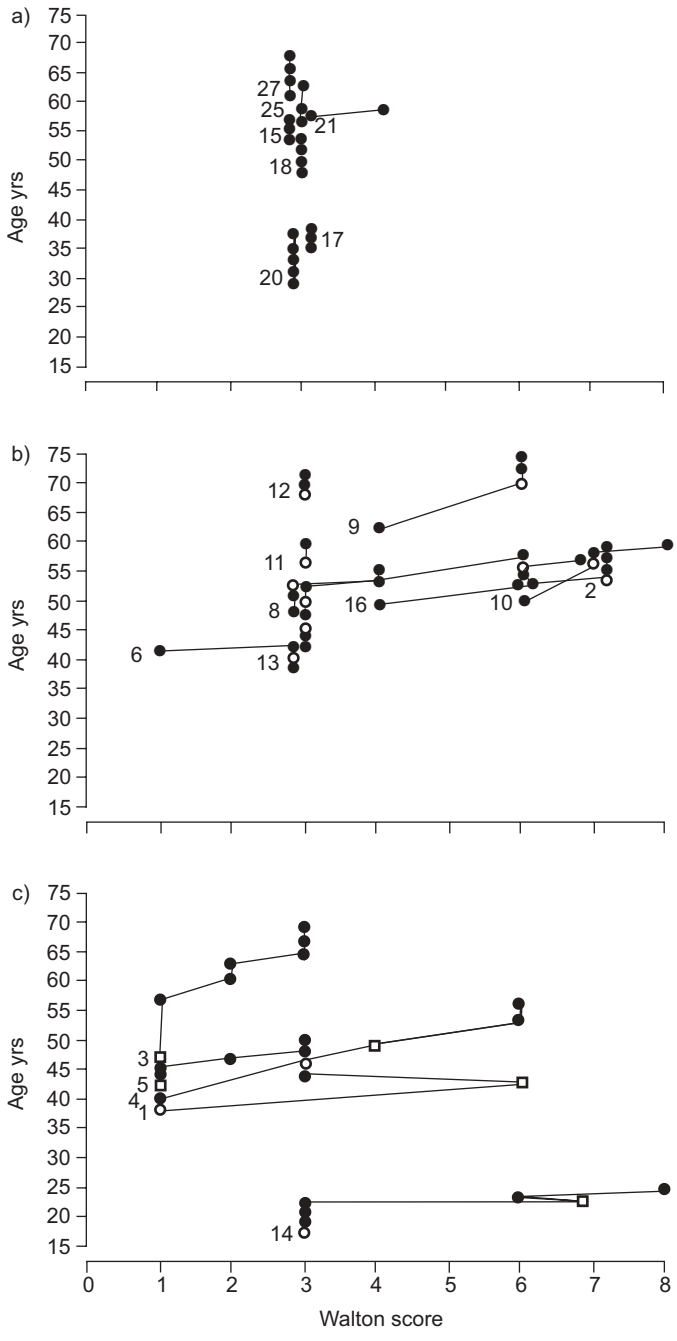

FIGURE 4. Individual results of Walton score changes with age. Each patient is individualised by its number (see table 1). a) Patients for whom mechanical ventilation and tracheostomy has not been indicated. b) Patients for whom noninvasive ventilation has been indicated, but not tracheostomy. c) Patients for whom tracheostomy has been indicated. ○: indicate the beginning of noninvasive ventilation; □: indicate the age of tracheostomy.

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