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Respiratory function in late-onset Pompe disease patients receiving long-term enzyme replacement therapy for more than 48 months

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Respiratorische Funktion unter Enzymersatztherapie über mehr als 48 Monate bei Patienten mit adultem M. Pompe

Zusammenfassung Die respiratorische Insuffizienz ist der wichtigste prognostische Faktor bei Patienten mit der adulten Form des M. Pompe. Der langfristige Erfolg einer Enzymersatztherapie auf die Atemmuskulatur ist noch nicht hinreichend belegt.

In unserer Studie wurden respiratorische Parameter (Vitalkapazität, VCmax; forcierte Einsekundenkapazität, FEV1; Peak flow, PEF) sowie die kapilläre Blutgasanalyse halbjährlich über einen Behandlungszeitraum von 48 bis 77 Monaten unter Enzymersatz bei sechs Patienten mit genetisch und biochemisch gesichertem late-onset M. Pompe erhoben. Außerdem untersuchten wir den Abfall der VCmax von aufrechter zu liegender Position, den maximalen Inspirationsdruck (PImax), den Mundverschlussdruck nach 100 ms (P0.1) und den Peak cough flow über 12 Monate. Nach 48 Monaten unter Enzymersatztherapie ergab sich dabei im Mittel eine Verbesserung um 8,8 % Punkte für ΔVCmax, +6,2 % Punkte für ΔFEV1 und +6,6 % Punkte für ΔPEF. Ein Patient zeigte nach initial rascher Verschlechterung der respiratorischen Parameter unter ERT eine Stabilisierung bis zum Monat 42 der Behandlung. Dennoch musste eine unterstützende Maskenbeatmung (NIV) aufgrund nächtlicher Sättigungsabfälle in der Polysomnographie initiiert werden. In den letzten 12 Monaten des Untersuchungszeitraums ließ sich eine wachsende Diaphragmaschwäche bei 3/6 Patienten nachweisen (Zunahme im Vergleich zum Ausgangswert im Median um 8 %).

Unsere Studie legt nahe, dass die Enzymersatztherapie in der Lage ist, die respiratorische Funktion bei erwachsenen Patienten mit M. Pompe zu stabilisieren und somit die Notwendigkeit einer Beatmung hinauszuzögern.

Schlüsselwörter: Adulter M. Pompe, Saure-Maltase-Defekt, Respiratorische Insuffizienz, Enzymersatztherapie, Neuromuskuläre Erkrankung

Summary Respiratory impairment is the most important prognostic factor in patients with adult-onset Pompe disease. The effect of long-term enzyme replacement therapy (ERT) on pulmonary function remains unclear.

Respiratory parameters (vital capacity (VCmax); forced expiratory volume (FEV1); peak expiratory flow (PEF); and blood gas analysis) were monitored every 6 months during a treatment period of 48–77 months of ERT in six patients with genetically and biochemically confirmed adult-onset Pompe disease. Postural drop of VCmax from sitting to supine position, maximal inspiratory muscle pressure (PImax), mouth occlusion pressure after 100 ms (P0.1), and peak cough flow (PCF) were measured over a period of 12 months. Mean change to baseline were +8.8 % points for ΔVCmax, +6.2 % points for ΔFEV1, and +6.6 % points for ΔPEF after 48 months of ERT. In one patient, a decrease of respiratory parameters with later stabilization was observed under ERT until month 42, but noninvasive ventilation (NIV) had to be initiated due to nocturnal desaturation. In the final 12 months period, progressive diaphragm weakness was detected in 3/6 patients (median change in VC% drop +8 %).

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ERT seems to stabilize pulmonary function and may delay the requirement for ventilation in patients with late-onset Pompe disease.

Keywords: Adult-onset Pompe disease, Acid maltase deficiency, Respiratory failure, Enzyme replacement therapy, Neuromuscular disease

Introduction

Pompe disease (glycogenosis type II) is a rare autosomal-recessive inherited metabolic myopathy and multisystemic disorder (OMIM # 232300) caused by lysosomal deficiency for α-glucosidase (GAA) [1]. Enzyme replacement therapy (ERT) with alglucosidase alpha for patients with the classical infantile and the late-onset type has been available since 2006 [2]. Late-onset Pompe disease is characterized by a progressive weakness of both limb-girdle and respiratory muscles. Respiratory failure is the leading cause of death in late-onset Pompe patients [3], but prognosis regarding respiratory impairment is highly complicated by the large interindividual variability in these patients. There is no clear correlation between severity of limb-girdle and respiratory involvement; one-third of adult patients require ventilator support while they are still able to walk [4]. On rare occasions, dyspnea can also be the first or even the only symptom in adult Pompe patients [5, 6]. Without ERT, pulmonary function measured by vital capacity declines in mean by 1.6 up to 4.6 % per year [7, 8] and assisted ventilation is commenced 15.1–19.4 years after the first symptoms of disease [9]. Therefore, monitoring the pulmonary function is essential in late-onset Pompe disease in order to evaluate the need for mechanical ventilation. In previous studies, 31–56 % of adult Pompe patients already required ventilator support when ERT was initiated [2, 10]. Long-term efficacy of replacement therapy is still uncertain. Therefore, the present single-center study on six adult Pompe disease patients assesses the respiratory function during ≥48 months of ERT treatment in a neuromuscular and pneumology clinic.

Patients, materials, and methods

Six adult patients were biochemically tested with reduced activity of α-glucosidase and genetically confirmed late-onset Pompe disease [11] and were monitored at the Department of Neurology at the Martin-Luther-University Halle-Wittenberg, Germany. The local Ethical Committee approved the protocol. Written informed consent was obtained from all patients. Each patient received biweekly intravenous infusions of recombinant human acid alglucosidase alfa (Myozyme™, Genzyme Corporation, Cambridge, MA, USA) at a standard dose regimen of 20 mg/kg body weight for at least 48 months without interruptions. Maximum vital capacity, forced expiratory volume, peak flow as percentage of predicted value were spirometrically assessed (body plethysmograph Jaeger labMax). Blood gas analysis (pO_2, pCO_2) was performed prior to and every 6 months during ERT. In the last year of therapy, postural drop of slow vital capacity from sitting to supine position (EasyOne™ diagnostic spirometer, ndd Medizintechnik AG, Zürich, Switzerland), maximal inspiratory muscle pressure (PImax in kPa), and mouth occlusion pressure after 100 ms (P0.1 in kPa) obtained by spirometry, and peak cough flow (PCF; l/min) by peak flow meter (Vitalograph™, Ennis, Ireland) as percentage of predicted value were obtained twice within a period of 12 months.

Results

Clinical data are summarized in Table 1. Mean time between first symptoms and beginning of ERT was 8.3 years (median: 11 ± 11 years). Total 3/6 patients requiring ventilation are described in detail below: In patient #1, respiratory failure without lung infection requiring invasive ventilation and tracheostomy at the age of 44 was the first symptom of Pompe disease. ERT was initiated 2 months after the first respiratory failure and tracheostoma was closed after 7 months of ERT. Ventilation continued noninvasively via biphasic positive airway pressure (BIPAP) for 2 h at daytime and 12 h at night. The patient is able to walk independently. Patient #4 had started nocturnal noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP) just a few months prior to commencing ERT. The first disease symptoms were limb-girdle weakness and dyspnea 5 years earlier. This patient is still mobile without assistance. Patient #5 with mild limb-girdle weakness started nocturnal noninvasive CPAP ventilation after 42 months of ERT due to desaturation in polysomnography. In upright spirometry, 4/6 patients showed stable or slight increase of VCmax during ERT, 1/6 had slight deterioration (Fig. 1, Table 2). Patient #5 showed continuously diminishing VCmax during the first 12 months of ERT, but then stabilized at this lower level. FEV1 was stable or improved in 3/6 and reduced in 3/6 during follow up. PEF was stable or improved in 4/6 and reduced in 2/6. Mean values for all patients and means of annual change under therapy were stable or slightly improved for all parameters at each time point (Table 2). Nevertheless, these changes were not significant. Postural drop of VC of more than 25 % was detected in 4/6 patients at baseline and 3/6 improved and 3/6 deteriorated within 12 months (Table 1). Blood gas analysis revealed no relevant CO_2 retention (Table 2). In the last 12 months of the observation period, PImax as an indicator of respiratory muscle weakness was improved or nearly unchanged in 3/6 patients. All tested patients had results within the normal range for P0.1 at baseline and after the observation period, indicating the absence of critical inspiratory muscle distress. For patient #5, no baseline value for P0.1 existed (Table 1). In PCF measurement, 2/6 patients improved, 2/6 remained nearly unchanged, and 2/6 deteriorated.

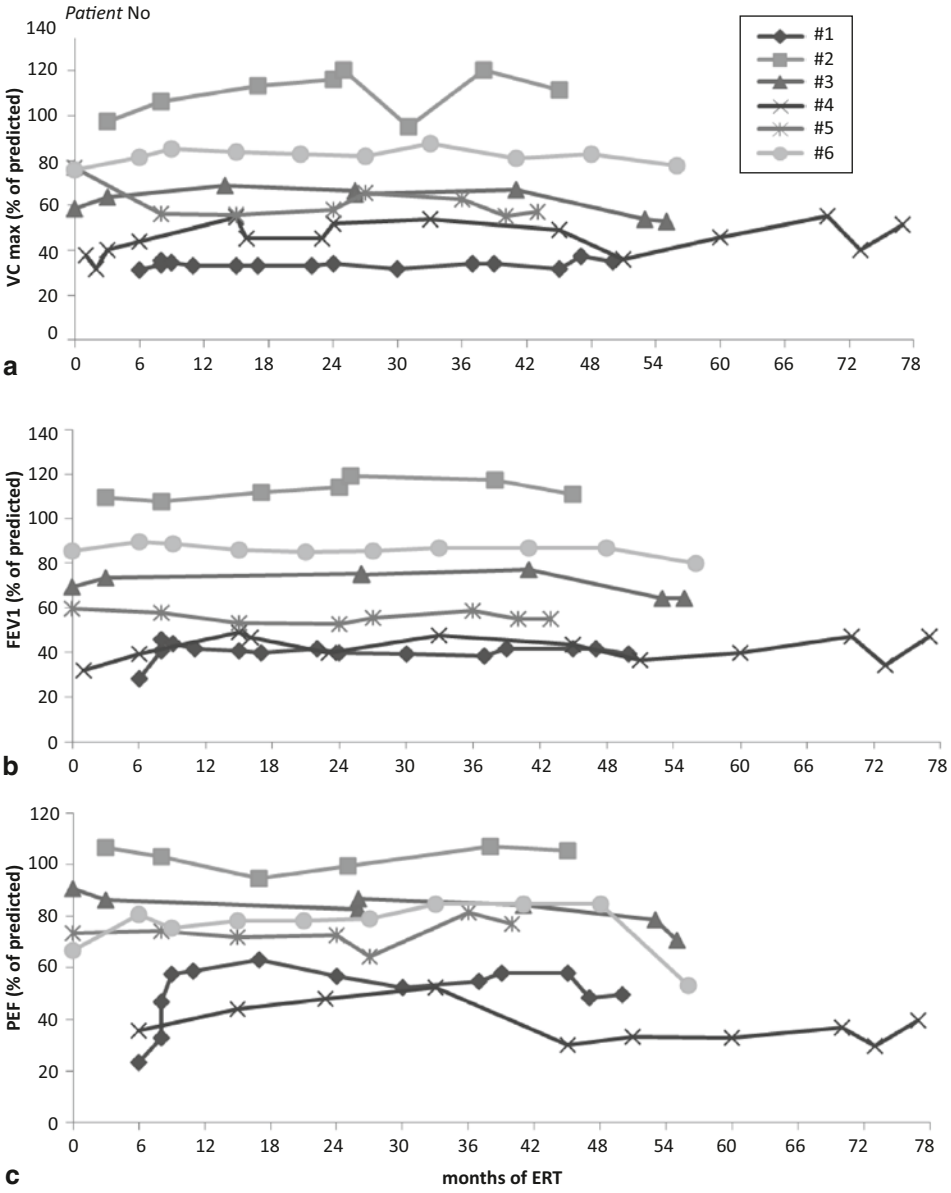

Fig. 1 Effects of ERT on respiratory function. Percentage of vital capacity (**a**), percentage of forced expiratory volume in the first second (**b**), and percentage of peak expiratory flow (**c**)

Discussion

In six late-onset Pompe patients, ERT resulted in stabilization or even slight improvement of pulmonary function measured by VCmax, FEV1, and PEF, consistent with other studies slight improvements in lung function during the first year of ERT [12, 13] and stabilization of VCmax following ERT for 36 months and longer in adult Pompe disease patients [14, 15]. In our study, efficacy of ERT was sustained for as long as 48 months for all six patients and even up to 77 months in one, but the effect appeared to fade over time. Due to the low number of patients, these effects were statistically not significant. Diaphragm weakness has been shown to occur in 38 % of untreated patients with Pompe disease with annual decrease of VC in sitting and supine position of 0.9 and 1.2 % points [16], respectively. In our patients, progressive diaphragm weakness was observed in one ventilated patient and predicted the need for NIV in another patient. The most prominent deterioration occurred in the oldest patient of our group. That may be the result of concomitant myalgia present in this patient. Pain occurs frequently in adult Pompe patients [10]. Other parameters of inspiratory muscles such as PImax and P0.1 showed rather inconsistent correlation to the patient's actual respiratory condition. This could be explained by the fact that these tests are difficult to perform and are highly dependent on patients' compliance. Therefore, our results favor the measurement of postural drop of slow VC rather than PImax and P0.1. as reliable tool for screening of inspiratory muscle strength, although most recently correlation of supine VC drop and invasive diaphragmatic indices has been questioned [17]. Assessment of diaphragmatic dysfunction using other parameters as esophageal pressure during forced inhalation (SNIFF), nasal pressure during inhalation (SNIP), or

Table 1. Epidemiology and clinical characteristics of patients

Patient number		#1	#2	#3	#4	#5	#6	Median *(p)*
Sex		Male	Female	Male	Male	Female	Female	
Gene mutation		IVS1-13T>G	45p. L552P	IVS1>13	IVS1-13T>G	IVS1-13T>G	IVS1-13T>G	
		c.2136-7 del GT	p-P493L	p.W499R	p.C.103G	p.L552P	IVS17-IVS18 del	
Age at first symptoms (years)		40	27	32	43	35	45	
Age at start of ERT (years)		40	34	39	48	45	66	
Duration of ERT (months)		50	48	56	77	43	56	
Ventilation mode (h)		NIV[a]	None	None	NIV	NIV[b]	None	
		BIPAP 14/24			CPAP 13.5/24	CPAP 12/24		
VC% predicted								
Sitting/supine	Baseline	32/17	106/95	43/24	36/22	51/33	80/73	58/44
	12 months	36/35	110/102	51/46	48/27	57/34	66/47	61/48
Postural drop percentage[c]	Baseline	47	10	56	39	34	9	33
	12 months	2	7	10	43	42	29	22
	Percentage of change	*−96*	*−30*	*−82*	*+10*	*+24*	*+220*	*+8* ($p=0.35$)
PImax kPa	Baseline	3.0	5.3	6.9	2.4	4.0	3.4	4.2
	12 months	3.0	8.1	7.1	3.6	4.2	4.0	4.7
	Percentage of change	*±0*	*+53*	*+2*	*+50*	*+5*	*+18*	*+8,3* ($p=0.35$)
P0.1[d]	Baseline	0.2	0.15	0.18	0.17	n.a.	0.3	0.2
	12 months	0.1	0.25	0.14	0.09	0.4	0.12	0.14
	Percentage of change	*−100*	*+66*	*−22*	*−47*	*n.a.*	*−60*	*−29* ($p=0.28$)
PCF percentage predicted	Baseline	41	74	56	43	56	46	53
	12 months	35	72	54	47	46	58	52
	Percentage of change	*−15*	*−3*	*−4*	*+9*	*−18*	*+26*	*−1* ($p=0.75$)

p significance in U-test Mann Whitney/Wilcoxon statistic analysis (statistically significant with $p \leq 0.05$), *NIV* noninvasive ventilation, *BIPAP* biphasic positive airway pressure, *CPAP* continuous positive airway pressure, *VC* slow vital capacity, *PImax* maximum inspiratory pressure, *P0.1* mouth occlusion pressure at 100 ms, *PCF* peak cough flow, *n.a.* not available

[a]Patient with initial tracheostoma

[b]Start of NIV at month 42 of ERT

[c]Percentage of drop of VC from sitting to supine position (normal <25 %)

[d]P0.1 normal <0.3

transdiaphragmatic pressure (Pdi) could be the alternatives [18, 19]. Impairment of PCF occurred in all patients demonstrating the deficient expiratory muscles and airway clearance, which further pulmonary infection [20]. However, none of the patients had a PCF sufficiently low to require a management with a mechanical insufflator/exsufflator device. In conclusion, the present study on adult Pompe patients suggests a stabilizing effect of long-term ERT on pulmonary function. This might even delay de novo ventilation in these patients. A close collaboration of neurologists and pneumologists is crucial for the treatment of adult Pompe patients and should be guaranteed in every neuromuscular clinic.

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Conflict of interest

Each author listed in this article has seen and approved the submission of this version of the article and takes full responsibility for this article. Drs. Schneider and Hanisch received reimbursement for attending a symposium. Dr. Hanisch and Prof. Zierz received fees for speaking and

Table 2. Spirometry (VCmax, FEV1, and PEF) and blood gas analysis (pO_2, pCO_2) under ERT

ERT (months)	Baseline	12	24	36	48	End of study
Percentage of VCmax[a]	63 (31–97)	67 (33–106)	68 (34–116)	66 (34–95)	69 (37–111)	64 (35–111)
Δ VCmax[b]		4.4 ± 12.2	5.3 ± 11.9	3.4 ± 9.9	8.8 ± 2.7	1.4 ± 11.6
p		0.35	0.35	0.35	0.35	0.67
Percentage of FEV1[c]	64 (31–97)	69 (42–108)	68 (40–114)	71 (39–119)	71 (40–111)	66 (39–111)
Δ FEV1[d]		6.0 ± 7,8	3.7 ± 5.9	7.0 ± 5.5	6.2 ± 4.5	2.1 ± 8.2
p		0.12	0.17	0.05*	0.11	0.75
Percentage of PEF[e]	66 (23–106)	74 (44–103)	73 (48–99)	77 (52–99)	71 (33–105)	66 (40–105)
Δ PEF[f]		10.0 ± 13.5	6.0 ± 15.2	10.5 ± 13.4	6.6 ± 12.6	– 0.1 ± 14.7
p		0.25	0.46	0.12	0.46	0.92
pO_2 (k Pa)[g]	9.7 ± 1.2	9.9 ± 2.3	8.8 ± 0.7	9.8 ± 0.9	10.1 ± 1.9	n.a.
pCO_2 (kPa)[h]	4.9 ± 0.4	5.1 ± 0.5	5.3 ± 0.4	5.1 ± 0.6	5.4 ± 0.8	n.a.

ERT enzyme replacement therapy, *p* Significance in U-test Mann Whitney/Wilcoxon statistic analysis, *VCmax* maximum of vital capacity, *FEV1* forced expiratory volume in 1s, *PEF* peak expiratory flow, *n.a.* not available

*$p \leq 0.05$

[a]Mean and range of VCmax as percentage of predicted
[b]Change of VCmax from baseline
[c]Mean and range of FEV1 as percentage of predicted
[d]Change of FEV1 from baseline
[e]Mean and range of PEF as percentage of predicted
[f]Change of PEF from baseline
[g]Normal values male 9.5–13.9 kPa
[h]Normal values male 4.7–6.1 kPa and female 4.3–5.7 kPa

organizing education. None of the other authors listed in this article has any potential conflict of interest to declare.

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