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Prognostic factors for the late onset Pompe disease with enzyme replacement therapy: From our experience of 4 cases including an autopsy case

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ABSTRACT

We report 4 cases of late onset glycogen storage disease type II (GSD II) or Pompe disease (OMIM #232300), under enzyme replacement therapy (ERT) with recombinant human acid alpha glucosidase (rh-GAA, OMIM *606800). In these 4 cases, we focused on the case of a 28-years-old man, whose condition at the ERT starting was the worst and resulted in poor prognosis. The autopsy was done under his family's permission, and revealed severe accumulation of glycogen in his muscle, especially diaphragm or iliopsoas, and pulmonary veno-occlusive disease (PVOD) which resulted in severe pulmonary hypertension (PH). This is the first report of PVOD as the cause of PH in Pompe disease. We studied this case comparing to another 3 cases of late onset Pompe disease under the same course of ERT in our hospital, and the average data of the group of late onset Pompe disease with severe pulmonary insufficiency receiving ERT, supposed that low score of the body mass index (BMI) on the baseline, the presence of specific genotype (p.R600C), and signs of pulmonary dysfunction suggesting PH (tachypnea, ultrasound cardiography data) were factors that influenced the prognosis. For a better prognosis in the late onset Pompe disease, an early diagnosis for the early start of ERT before the onset of respiratory failure should be important, and the deliberate management and care should be needed even after the ERT start, especially for severe cases including pulmonary dysfunction.

Introduction

Pompe disease, caused by the deficiency of acid alpha glucosidase (GAA) was reported by Pompe in 1932 [1], and proved by Hers in 1963 [2]. The incidence has been reported as 1/40,000 in the world. A-GAA cDNA is 3.6 kb coding 952 amino-acid. The gene includes 20 exons, located in 17q25.2–25.3, and more than 200 mutations have been reported. The clinical course had been reported as progressive and lethal, especially juvenile type [3]. Recently, the recombinant GAA (rGAA) was developed using Chinese hamster ovary (CHO) cells and the ERT using this recombinant enzyme has been started in many countries. In some clinical trials, the ERT proved to be drastic effective especially in the severe juvenile type and some cases of late onset type [4]. Here we report the outcome of 4 patients with late onset Pompe disease who were under ERT, including the index case which resulted in autopsy, and try to estimate the causes of his poor prognosis.

Methods

Recombinant GAA (rGAA), Myozyme™, developed by Genzyme corporation using Chinese hamster ovary cell, was used in the ERT for these 4 Japanese patients. After initial study including genotyping, rGAA was injected by drip infusion of 20 mg/kg biweekly for the 4 patients diagnosed as late onset Pompe disease; their profiles are shown in Table 1. Patients are evaluated at some time points as 6, 12, 20 months after ERT started, including manual muscle test (MMT), arm and leg functional scores [5,6], and Walton and Gardner-Medwin scale (W&G scale) [7], echocardiography, and blood examination. MMT is assessment of muscle strength performed to determine the ability of a muscle or muscle group to function in movement

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Table 1
Profiles of 4 patients and average data of expanded Access Program (EAP, by Genzyme Co., $n = 5$) of this study was shown. In EAP, NIV rate decreased (from 40% to 20%) in 12 months with ERT.

Profile		Case 1	Case 2	Case 3	Case 4	EAP
Sex		Male	Female	Female	Male	Male 40%
Age of onset		4	4	13	13	7.8
Age of ERT starting		28	17	36	44	24.8
Therapy-off period		24	13	23	29	17
Familial history		None	None	Father as Pompe disease	Parents as consaguinous marriage	
Genotype		R600C/M439K	R608X/c.546G > T	R600C/c.546G > T	c.546G > T/c.546G > T	
Condition on baseline	BMI	9.7	18	19	21.3	11.5*
	Respiration	NIV	n.d.	n.d.	n.d.	NIV 40% IMV 60%
	Compilation	PT, SMAS	None	None	None	
Outcome at 12 month	Respiration	IMV	Normal	Normal	Normal	NIV 20% IMV 80%
	Compilation	PH, pneumonia	None	None	None	
	General	Deceased (29 years)	Alive	Alive	Alive	20% (5.4%)**

BMI, body mass index; NIV, non-invasive ventilation; n.d., nocturnal dyspnea (mild); PT, pneumothorax; SMAS, superior mesenteric artery syndrome; IMV, intermittent mechanical ventilation (tracheotomy); PH, pulmonary hypertension.
* BMI score of EAP group was significant lower than the score of the case 2–4, as the group without severe respiratory insufficiency ($p = 0.0028$, by t-test, each data of EAP not shown).
** The mortality of EAP group was 20% (1/5, this patient is the index case of this study), comparing the data in the parenthesis, as the mortality of 5.4% in all late onset Pompe disease.

and to provide stability and support (Fig. 1A). It is recommended that MMT will be performed in the sitting, prone, side lying and supine positions, in which larger grade means better score. In this study the data was represented by the score in the sitting position. Arm and leg functional scores, and W&G scale are originally used for evaluating the natural progression and efficacy of treatment of Duchenne muscular dystrophy, in which smaller grade means better score, i.e. grade 0 means pre-clinical, all activities available in W&G score (Fig. 1B). The evaluating of these scores or scales was done by the specialist of rehabilitation.

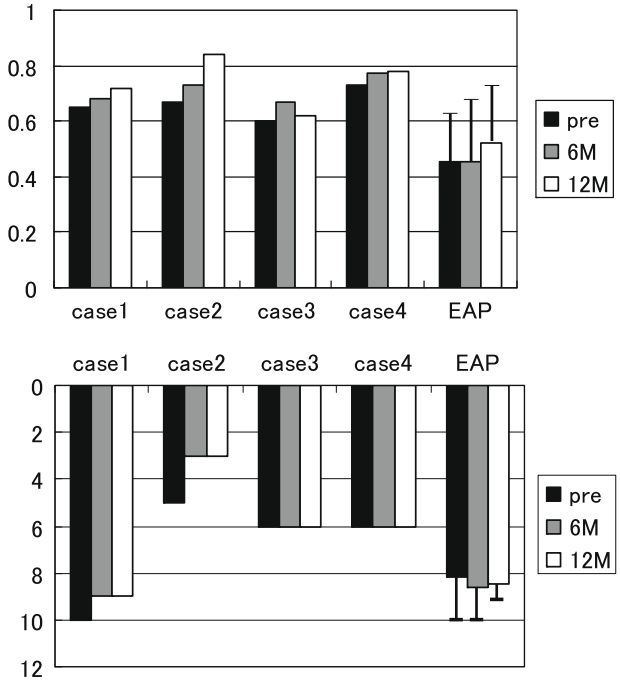

Fig. 1. (a) MMT (manual muscle test) score as summarized of all part at various positions for rate to normal (1.0 as 100%). All four patients and EAP average score showed improvement in time course. (b) W&G (Walton and Gardner-Medwin) scale, in which smaller grade means better score, i.e. grade 0 means pre-clinical [7]. Only the case 2 showed improvement, another patients showed no change or getting worse.

In this study, we focused on the case 1 (Table 1) as the index, because his general condition was the worst among these 4 patients, and resulted in death. The autopsy revealed some important prognostic factors for his poor outcome. We got the agreement for publication of the clinical data from all these patients and their families before the beginning of this study under the approval of the ethical committee in the Jikei University School of Medicine.

Results

Case 1, *the index case*, was 29 years-old at the ERT starting point, Japanese man, with the onset of symptoms at 4 years of age as difficult for climbing stairs, and had been suffering from dyspnea and morning headache as reflection of hypoxia since 19 years-old. He had also past history of frequent episodes of pneumothorax and superior mesenteric artery syndrome, both should be from his severe emaciation. Despite the improvement of pneumothorax after the pleurodesis, he presented multiple blebs and fibrosis on CT scan and enlarged esophagus on X-ray (Fig. 2). His genotype was R600C/M439K, the former has been reported as common in Japanese, and severe mutation. We started rGAA ERT for him biweekly, and he has shown some improvement in MMT score, but not in W&G scale (Fig. 1), and deterioration in respiratory function. On baseline, his nutrition markers themselves were not so bad, as total protein (TP) 7.6 g/dl, Albumin (Alb) 4 g/dl, Calcium (Ca) 9.0 mg/dl, suggesting that his emaciation was not from malnutrition but thought to be from autophagic mechanism. Creatine Kinase (CK) was higher than normal range, but got better after 18 months with ERT. And his respiratory state had been poor or chronic hypercapnia (pCO2 61.4 mmHg on baseline) and we could not improve finally. Eighteen months after ERT starting, he has hospitalized for almost one month due to an aspiration pneumonia, and recovered after one month hospitalization receiving antibiotics as Meropenem. But 2 weeks later, he had severe pneumonia again, needed tracheal intubation in emergency. Escaping the narrow crisis with intensive care, he left the ICU one month after the admission. His general symptom got better, but developed tachypnea which got slowly progressive worse arising the clinical suspicion of pulmonary hypertension. It was supported by the study of ultrasound cardiography (UCG) as the right ventricular dilatation (RVH) and high score (more than 40 mmHg) of ΔPG, pressure gradient between