The FAbry STabilization indEX Is Insufficient for Evaluating the Effectiveness of Enzyme Replacement Therapy for Pediatric Fabry Disease

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Review

The FAbry STabilization indEX is Insufficient for Evaluating the Effectiveness of Enzyme Replacement Therapy for Pediatric Fabry Disease

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Abstract: ***Background*:** Fabry disease (FD) is a progressive disorder characterized by a decrease or deficiency in α-galactosidase enzyme activity. The FAbry STabilization indEX (FASTEX) scores FD symptoms and measures clinical deterioration as the score increases. However, the effectiveness of FASTEX for evaluating pediatric FD has not yet been examined. ***Methods**:* We conducted FASTEX scoring on 5 cases of FD receiving enzyme replacement therapy at our department by September 2022 (1 classical-type male, 2 late-onset males, and 2 heterozygous females). We performed FASTEX scoring before and after the initiation of treatment, defining a change in score of 20% or less from the baseline as clinically unchanged. ***Results:*** FASTEX did not show an increase in scores during the treatment course in the late-onset males and heterozygous females. FASTEX in the classical-type male only increased from 0 to 5 points during treatment, but did not show a temporal increase and, thus, he was judged to be clinically unchanged. ***Conclusion:*** FASTEX may not be sufficient to evaluate treatment effects in pediatric FD cases. New evaluation methods for pediatric cases are required, particularly for those detected through newborn screening.

Keywords: children; ERT; GL-3; *GLA*; globotriaosylceramide; lysosome

1. Introduction

Fabry disease (FD) is a progressive, X-linked inherited disorder characterized by a decrease or deficiency in α-galactosidase enzyme activity, resulting in various symptoms [1]. Symptoms include skin lesions, peripheral neuropathy, stroke, arrhythmias, cardiomyopathy, renal failure, and other complications [1]. The signs and symptoms of this progressive disease typically begin in childhood and include skin lesion, gastrointestinal symptoms, and peripheral neuropathy. End-organ involvement, including kidney dysfunction, and cardiac involvement typically in adulthood [2].

Enzyme replacement therapy (ERT) was approved for the treatment of FD in the USA and EU in 2001 and in Japan in 2004. Newborn screening (NBS) for FD has been performed since August 2006 in the western region of Japan [3]. The prevalence of FD in Japan was previously reported to be 1/7057 [4].

Two disease severity scoring system for FD, the Maintz Severity Score Index (MSSI) and Fabry Disease Severity Scoring System (DS3), have been validated [5, 6]. These two scores provide an index of disease severity at a single point, and do not allow evaluation of the clinical course over time. Clinical stability of treated patients is indicative of the efficacy of ERT, and untreated patients who became clinically unstable may need to be initiated on treatment with ERT. FAbry STabilization indEX (FASTEX) scores are an innovative tool for the assessment of FD symptoms and measures

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clinical deterioration as the score increases [7]. FASTEX is proposed that may allow quick and easy estimation of disease stability or progression for FD in adults. Accurate assessment of clinical stability and evaluation of ERT efficacy is essential, even if clinical symptoms are poor in pediatric patients with FD. However, the effectiveness of FASTEX in pediatric FD patients has not yet been examined.

Therefore, the present study investigated the potential of FASTEX as a tool to assess the effectiveness of treatment for pediatric FD patients.

2. Materials and Methods

We conducted FASTEX scoring on 5 FD cases receiving ERT at our department by September 2022 (1 classical-type male, 2 late-onset males, and 2 heterozygous females). Average age at the start of treatment was 11 years, and the average duration of treatment was 3.4 years. The characteristics of these cases are shown in Table 1.

We used FASTEX to evaluate the following domains: nervous system; pain, cerebrovascular events, renal; proteinuria and/or urinary albumin excretion, estimated glomerular filtration rate (eGFR), and cardiac; echocardiography parameters, electrocardiograph parameters, New York Heart Association (NYHA) class (Table 2). We performed FASTEX scoring before and every six months to one year after the initiation of treatment (Table 3). We defined a change in score of 20% or less from the baseline as clinically unchanged.

3. Results

Case 1 was a 16-year-old girl. She had a family history of FD, was diagnosed, and *GLA* gene testing revealed the M43V variant. She had mild leg pain on exercise, urinalysis indicated Mulberry bodies, and renal biopsy showed Gb3 accumulation in podocytes by electron microscopy (Figure 1-A). ERT with agalsidase beta was initiated at the age of 12 years. Pain in the extremities improved after the initiation of ERT, and FASTEX scores decreased from 5 to 0.

Case 2 was a 17-year-old girl. She had a family history of FD, was diagnosed, and *GLA* gene testing revealed the R220X variant. Urinalysis indicated Mulberry bodies and renal biopsy showed Gb3 accumulation in podocytes by electron microscopy (Figure 1-B). ERT with agalsidase alpha was initiated at the age of 14 years. No changes were observed in symptoms following the initiation of ERT and FASTEX scores were 0.

Case 3 was a 9-year-old boy. He was diagnosed with FD as a result of NBS and GLA gene testing revealed the G43D variant. The initiation of ERT was scheduled once FD symptoms manifested. Mulberry bodies were noted on urinalysis prior to treatment initiation. ERT with agalsidase alpha was started at the age of 6 years. No clinical symptoms were observed before ERT; however, pain in the extremities developed during ERT. FASTEX scores increased from 0 to 5 before ERT for peripheral neuropathy. However, there was no further increase during ERT and, thus, he was judged to be clinically unchanged.

Cases 4 and 5, a 13-year-old boy and 12-year-old boy, were siblings. They were diagnosed as a result of NBS and GLA gene testing revealed the V199M variant. Renal biopsy identified zebra bodies in podocytes by electron microscopy (Figure 1-C and 1-D) and ERT was started at the ages of 12 and 11 years. There were no clinical manifestations during ERT and FASTEX scores were 0.

Figures, Tables and Schemes

Figure 1-A shows the electron microscopy results of the renal biopsy of Patient 1, Figure 1-B shows Patient 2, Figure 1-C shows Patient 4 and Figure 1-D shows Patient 5, respectively. Zebra bodies can in podocytes by electron microscopy be seen in all cases.

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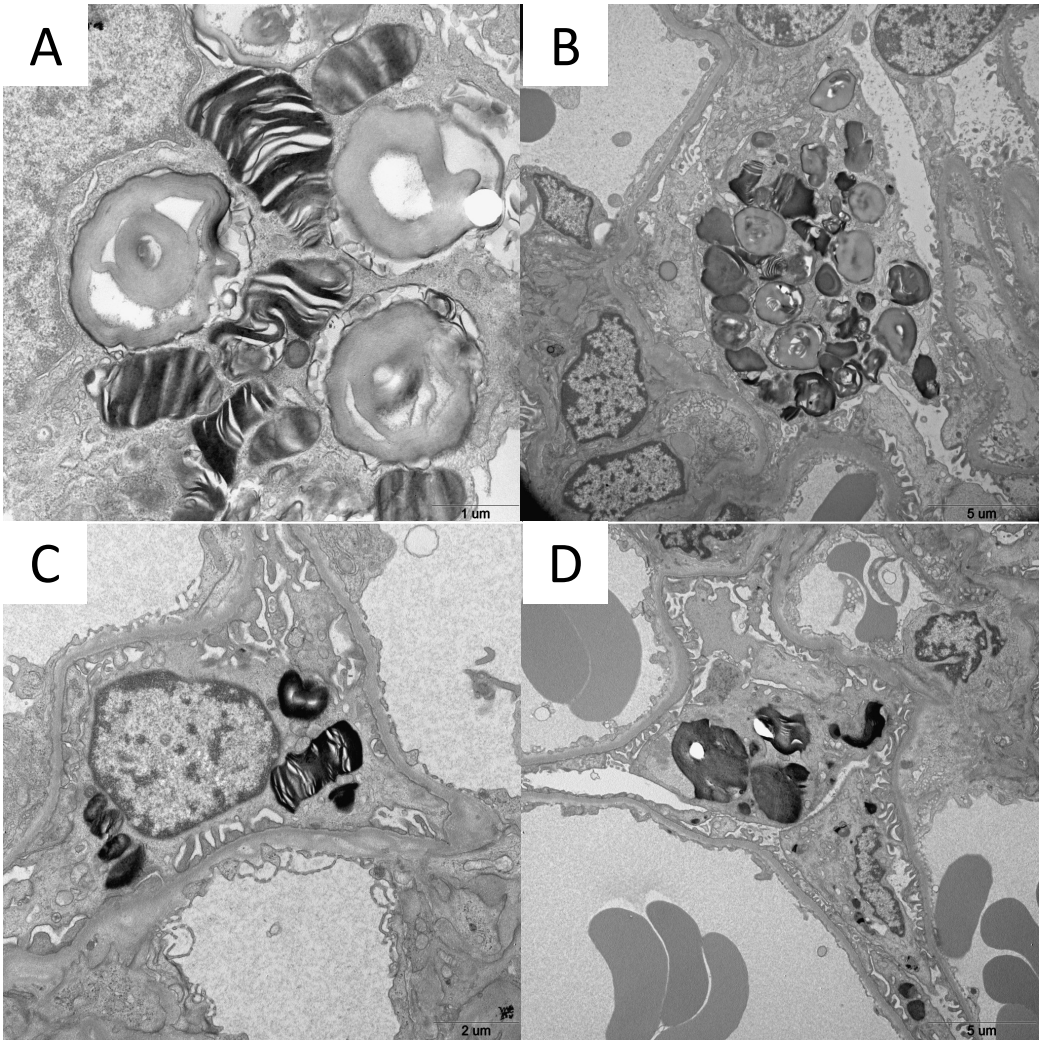

Figure 1. Results of renal biopsies before ERT initiation.

Table 1. Characteristics of FD patients in this study.

Case No.	Sex	Age	Genotype	Phenotype	Diagnostic opportunity	Symptoms before ERT	Age at starting ERT	Duration on ERT (year)	Type of agalsidase
1	F	16	M43V	heterozygous	family history	extremities pain	12	4	beta
2	F	17	R220X	heterozygous	family history	none	14	3	alpha
3	M	9	G43D	classical	NBS	none	6	3	alpha
4	M	13	V199M	late onset	NBS	none	12	1	beta
5	M	12	V199M	late onset	NBS	none	11	1	beta

Table 2. FASTEX scoring methods.

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score	assesment	Weighted score							
		0	5	10	20	25	30	35	40
Nervous	pain	None	Mild without treatment		Moderate without treatment				Present and controlled with therapy
	Events	None		Hyperintensity of white matter			TIA		
Renal	eGFR (ml/min/1.73m^2)	>90-<135		>135					
	ACR/ PCR (mg/g)	ACR <22 (or <2.5 mg/mmol)						ACR 22-299 (or 2.5-29 mg/mmol)	
Cardiac	LVH	No LVH		Diastolic dysfunction					Mild LVH (11.5-13.5 mm)
	ECG/arrhythmia	None				Short PQ, ST alteration			45 LVH on ECG
	NYHA class	0							1

score	assesment	Weighted score							
		50	55	60	65	70	80	90	100
Nervous	pain								Present and not controlloed with therapy
	Events			ischaemic or haemorrhagic					Reccuremt TIA or stroke
Renal	eGFR (ml/min/1.73m^2)	60-<90					30~59		<29
	ACR/ PCR (mg/g)		PCR >300-499		PCR >500~799				PCR >800
Cardiac	LVH					Moderate LVH (>13.5-15 mm) or Fibrosis MRI			Severe LVH (>15 mm)
	ECG/arrhythmia					AVB, PSVT, AF, NSVT, bradycardia			PM, ICD
	NYHA class			2			3		4

AVB, atrio-ventricular block; AF, atrial fibrillation; ACR, urinary albumin: creatinine ratio; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); ECG, electrocardiogram; ICD, implantable cardiac defibrillator; LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; PCR, urinary protein: creatinine ratio; PM, pacemaker; PSVT, paroxysmal supraventricular tachycardia; TIA, transitory ischaemic attack.

Table 3. Change of FASTEX score.

Case No.	bofore ERT	visit1	visit2	visit3	visit4	visit5	outcome
1	5	0	0	0	0	0	unchanged
2	0	0	0	0	0	–	unchanged
3	0	0	5	5	5	5	unchanged
4	0	0	0	0	0	0	unchanged
5	0	0	0	0	0	0	unchanged

4. Discussion

The present study examined the effectiveness of FASTEX for evaluating pediatric FD treated with ERT. The obtained results showed that scores did not increase in heterozygous FD females (cases 1 and 2) or late-onset FD males (cases 4 and 5). Although the male with classical-type FD (case 3) developed neuropathic pain during ERT, he was judged to be clinically unchanged based on his FASTEX scores. These results suggest that FASTEX is inadequate for evaluating pediatric FD during ERT. FASTEX assesses neurological, cardiac, and renal symptoms [7]; however, the clinical symptoms of pediatric FD include neuropathic pain and gastrointestinal dysfunction [8, 9].

On the other hand, biomarkers associated with FD, such as Lyso-Gb3, which are considered to be diagnostically useful [10], have been shown to rapidly decrease after the initiation of ERT [11]. In addition, the formation of anti-drug antibodies to enzyme preparations adversely affects the decline in biomarkers [11]. The positive rate of antidrug antibodies is as high as 57% in classical-type FD patients, and Lyso-Gb3 levels do not markedly decrease in antibody-positive patients, in contrast to antibody-negative patients [12], suggesting that the monitoring of antidrug antibodies is also important for male patients with classical-type FD, such as case 3. Therefore, the measurement of biomarkers and anti-drug antibodies may be more useful for evaluating the treatment course of pediatric FD patients after the initiation of ERT than FASTEX scoring. However, these measurements are not currently covered by the national health insurance system in Japan.

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In addition, FD has variable symptoms and is a progressive disease [13]. Organ damage may be irreversible if treatment is delayed [14]. A previous study reported that the duration of time between the onset and diagnosis of FD ranged between 25 and 36 years, with FD being diagnosed in patients in their 40s, even though it develops in teenagers [15]. Some regions in Japan have begun to detect FD through NBS and, thus, the number of pediatric FD patients is expected to increase in the future. The guidelines for FD suggest the initiation of ERT for males with classical-type FD who develop pain in the extremities and late-onset FD males and heterozygous FD females with organ damage [1, 16]. However, in the future, FD patients identified in NBS may begin ERT before symptoms develop.

Based on the present results, FASTEX evaluations of asymptomatic FD patients detected in NBS and receiving ERT may be insufficient. New methods, such as biomarkers and pediatric-specific scoring, need to be developed for the management of FD from childhood when clinical symptoms are less likely to appear.

5. Conclusions

FASTEX is a good tool for evaluating FD, but may be insufficient for assessing treatment effects in pediatric FD cases. New evaluation methods for pediatric cases are required, particularly those identified in NBS.

6. Patents

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Informed Consent Statement: Informed consent was obtained from all patients involved in the study to publish this paper.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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