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First 2 Fabry Cases with Novel Mutation and Their Associated Clusters in Malaysia

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Case series

Patients: Male, 39-year-old (age at diagnosis) • Male, 62-year-old (age at diagnosis)
Final Diagnosis: Fabry disease
Symptoms: Corneal verticillata • kidney failure • neuropathy • proteinuria
Medication: —
Clinical Procedure: —
Specialty: Genetics • Hematology • Laboratory Diagnostics • Nephrology • Neurology • Ophthalmology**Objective:** Rare disease**Background:** No cases of Fabry disease (FD) have been reported thus far in Malaysia. We aimed to report the demographic characteristics, clinical manifestations, molecular results, and treatment outcomes of 2 FD cases. This study was a retrospective review of 2 family clusters of FD on follow-up in Sarawak, Malaysia.**Case Reports:** Two index patients were confirmed to have FD. Index patient 1, who had nephrotic-range proteinuria and cornea verticillata, carried a variant within exon 4 of the *GLA* gene: c.610 T>C (p.Trp204Arg). Agalsidase beta (Fabrazyme®) enzyme replacement therapy was initiated, with the absence of neutralizing antibody after 24 months. No hypersensitivity or adverse reactions were reported. The patient's proteinuria and renal function remained stable. Other family members who carried the same mutation were asymptomatic. Index patient 2, who had residual activity of α -galactosidase A and a normal globotriaosylsphingosine level, carried a novel *GLA* mutation of c.548-5T>A. He was diagnosed with end-stage renal disease on regular dialysis and had nonspecific headache with 1 episode of seizure a few years prior to FD genetic screening. One brother had chronic neuropathic pain but refused further investigations. Other family members who had the same mutation were asymptomatic. This mutation has never been reported in literature, and its pathogenicity warrants further studies.**Conclusions:** It is of utmost importance to increase awareness of FD among clinicians, so that appropriate screening may be done to determine its true prevalence and prompt treatment can be initiated early.**Keywords:** Enzyme Replacement Therapy • Fabry Disease • Malaysia • MutationFull-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932923> 2594 1 2 28

Background

Fabry disease (FD), an X-linked recessive lysosomal storage disorder of glycosphingolipid catabolism, results from deficient or absent activity of the lysosomal enzyme α -galactosidase A (α -gal A). The enzymatic defect leads to progressive accumulation of the glycolipid globotriaosylceramide (GB3 or GL3) and globotriaosylsphingosine (lyso-GL3 or lyso-Gb3) in the lysosomes in the cells of most organs, leading to selective multi-organ damage affecting the kidneys, heart, nervous system, eyes, vascular, and other systems [1,2].

The incidence of FD varies widely in different countries, and it can present in many variant forms. In some countries such as Taiwan, FD is part of a universal newborn screening program [3]. In contrast, Malaysia has restricted diagnostic kits and limited accessibility to treatment. To our knowledge, no cases of FD have been reported thus far in Malaysia. We report 2 cases of FD in Sarawak, Malaysia, along with their demographic characteristics, clinical manifestations, treatment options, and outcomes. We also aimed to identify family clusters through enzyme testing and genetic screening. We hope to increase awareness of the disease, so that appropriate screening may be done to determine its true prevalence and appropriate treatment can be initiated early.

This study was a retrospective review of 2 cases of FD diagnosed in Miri Hospital, Sarawak, Malaysia. The family members of the 2 index cases were subsequently identified and counseled regarding the disease and its genetic transmission. If they consented, they were tested for the enzyme and glycolipid levels. If the levels were found to be abnormal, the family members then underwent further genetic testing. Informed written consent was obtained from each participant in compliance with the requirements of good clinical practices. All participants were screened in Miri Hospital and Sarawak General Hospital between January 2018 and September 2020. The results of the tests were communicated to the participants and further counseling was given if needed.

In this study, we analyzed the data of our FD patients and aimed to elucidate their molecular, biochemical, and clinical characteristics. Data were collected in English using a standardized form (available online and on paper), quality checked, and reviewed. Demographic data collected included age at the time of FD diagnosis, sex, ethnicity, family pedigree, and consanguinity. Clinical data pertaining to FD comprised types of genetic mutation, α -gal A enzyme activity, lyso-GL3 biomarkers, renal profile (biochemistry, urinalysis, and imaging), cardiac parameters (12-lead electrocardiogram, pro-B-type natriuretic peptide [pro-BNP], and echocardiography) as well as findings from slit-lamp examination, audiogram, and sensory, neurological, and cutaneous examinations. Targeted neurological

investigations were performed when clinical neurological manifestations were present. The types of treatment received, related adverse events, and clinical response were also included in the analysis.

α -gal A enzyme activity and concentration of lyso-GL3 biomarkers were tested using tandem mass spectrometry methods from dried blood spot samples. Disease-causing mutations in the *GLA* gene were assessed using DNA extraction from dried blood spot, which underwent PCR amplification and sequencing of all coding exons flanking intronic regions. All diagnostic tests were standardized and performed in ISO 9001: 2008 certified ARCHIMED laboratories in Vienna, Austria. Throughout this article, we refer to the *GLA* reference sequence: GenBank NM_000169.2 (ENST00000218516). Anti-drug (Fabrazyme) immunoglobulin G (IgG) and neutralizing antibody tests were run at LabCorp (Burlington, NC, USA).

Transthoracic echocardiography studies were performed by the same experienced echocardiographer for all patients in the left lateral decubitus position, using Philips HD 15 and transducer S5-2 Adult sector. The HD15 included Philips QLAB quantification software, XRES image processing, and PureWare transducer crystal technology. The standard evaluation included M-mode, 2-dimensional (2-D), and Doppler studies according to the American Society of Echocardiography recommendations [4]. Left ventricle (LV) ejection fraction was calculated from apical 4-chamber views using Simpson's method. The maximum LV wall thickness was defined as the greatest end-diastolic thickness in any myocardial segment. The LV end-diastolic diameter and end-systolic diameter were measured from M-mode and 2-D images obtained from parasternal long-axis views. The LV mass index was calculated using Devereux's formula.

Case Reports

Index patient 1 was a 46-year-old man who presented with intermittent frothy urine and bilateral lower limb swelling when he was 35 years old in 2009. Investigations then showed proteinuria of 1 g/d; his blood pressure and renal function were normal. There was a progressive increase in proteinuria on follow-up, and a kidney biopsy was done 4 years later. The biopsy specimen was assessed using light microscopy and immunofluorescence study by a renal pathologist. Prominent podocytes with abundant foamy cytoplasm were found on histopathological examination and staining for immunoglobulin (Ig) G, IgA, IgM, and complement were negative. Further clinical details are shown in **Table 1**.

Index patient 1 was found to have cornea verticillata (**Figure 1**). He did not take concomitant medication at any time in the medical history that might have induced such eye findings, such

Table 1. Diagnosis, characteristics, and clinical presentation of index patients with Fabry disease.

	Index patient			Index patient	
	1	2		1	2
Age at diagnosis, y	39	62	GLA mutation	c.610 T>C [p.Trp204Arg]	c.548-5T>A
Ethnicity	Malay	Chinese	Phenotype	Classic	Unknown
CKD stage at diagnosis (KDIGO classification criteria)	3b	5	Kidney biopsy	+	NP
eGFR (CKD-epi formula), mL/min/1.73 m ²	39	5	Pro-BNP, pg/mL	821	>9000
Daily protein loss, g	3.15	Anuria	Echocardiography findings		
Dialysis dependent	–	+	Patterns of LVH	Concentric	Concentric
Hypertension	–	+	Interventricular wall thickness, mm	13.5	14.4
Angiokeratoma	+	–	Posterior wall thickness, mm	14.4	16.1
Neuropathy/acroparesthesia	–	–	LV end-diastolic diameter, mm	49.1	51.8
Eye abnormalities	Cornea verticillata	–	LV end-systolic diameter, mm	31.3	31.9
Gastrointestinal symptoms	–	–	Ejection fraction, %	64.5	65.1
Cerebrovascular	–	–	LV mass index, g/m ²	177	270
Hypohydrosis	–	–	Number of affected relatives	7	5
Time of first symptoms until DBS, y	9	4	On enzyme replacement therapy	Yes (Fabrazyme® (agalsidase beta), 1 mg/kg every 2 weeks)	No
GLA activity,* μmol/L/h	0	2.4			
Lyso-Gb3 level,** ng/mL	22.0	1.2			

‘–’ – negative; ‘+’ – positive; CKD – chronic kidney disease; DBS – dried blood spot; eGFR – estimated glomerular filtration rate; KDIGO – Kidney Disease: Improving Global Outcomes; LV – left ventricle; NP – not performed; Pro-BNP – pro-B-type natriuretic peptide. * Reference value: ≥ 2.8 μmol/L/h; ** Reference value: ≤ 3.5 ng/mL.

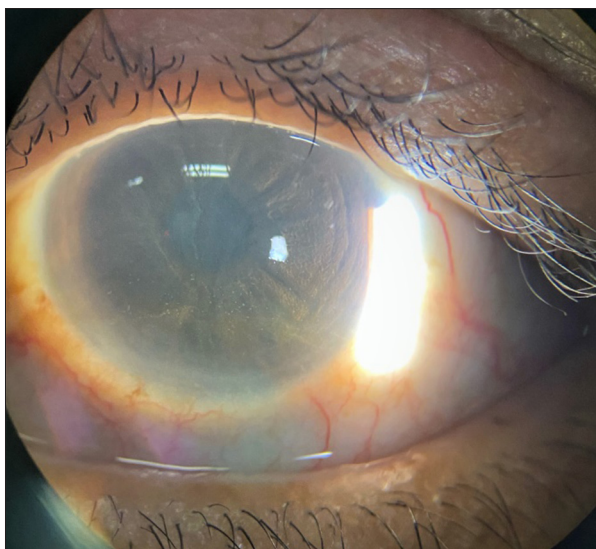


Figure 1. Cornea verticillata found in the left eye of index patient 1.

as chloroquine, amiodarone, and nonsteroidal anti-inflammatory drugs. Echocardiogram showed concentric left ventricular hypertrophy (LVH) with preserved ejection fraction. Family screening of this index patient was done and another 7 family members were found to have the enzyme abnormalities and genetic mutation (Figure 2). They were asymptomatic at the time of data collection.

Enzyme replacement therapy (ERT) was initiated in this patient in 2018, 5 years after the biopsy and after a delay of almost a decade since the first clinical manifestation of frothy urine and limb swelling. After 24 months of ERT, the agalsidase beta IgG antibody titer was 3200, while the neutralizing antibody was undetectable. The patient tolerated ERT well without developing hypersensitivity or adverse reaction. His proteinuria and renal function remained stable since the commencement of ERT.

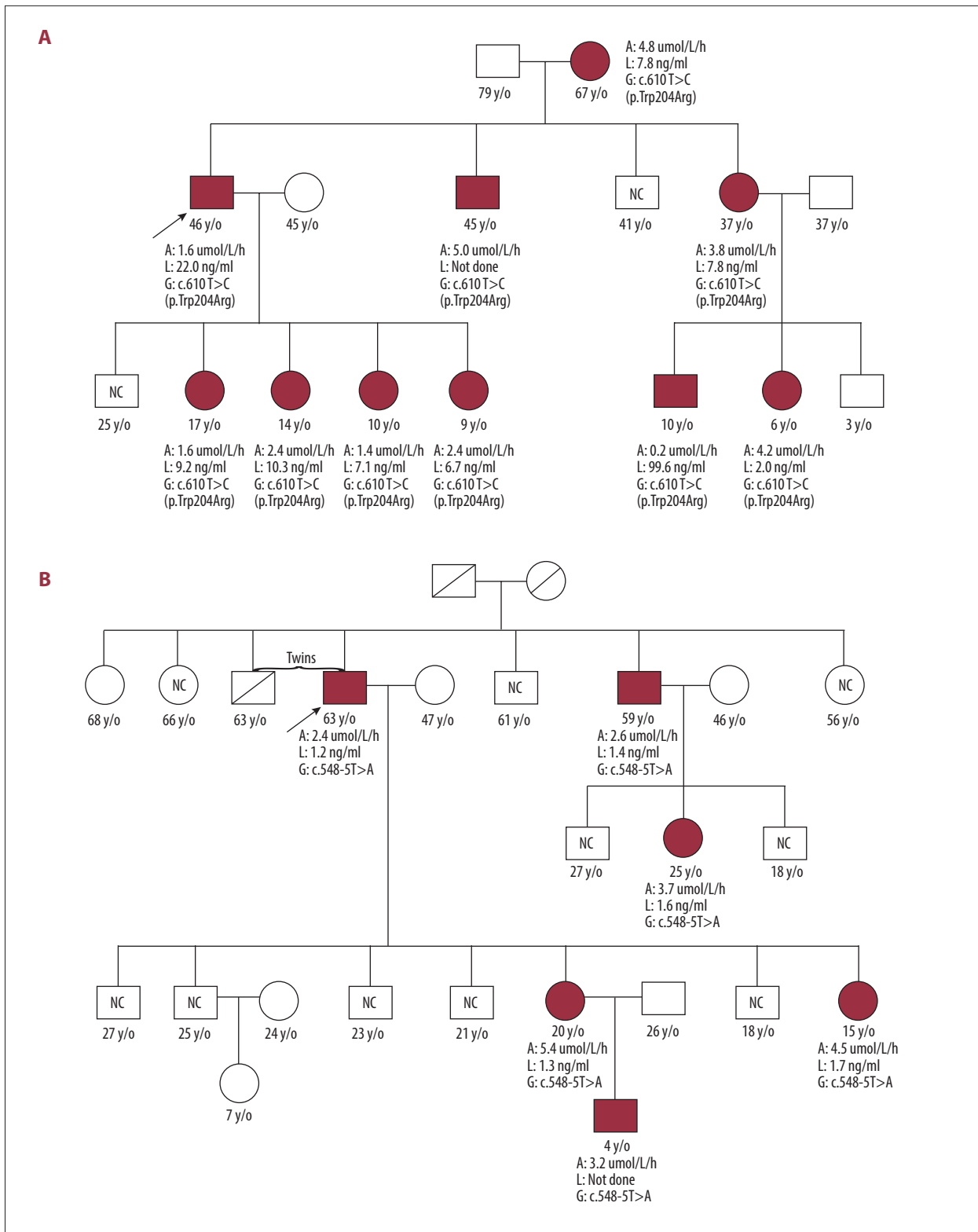


Figure 2. The results of family screening and pedigree from index patients 1 and 2. The index patient is marked by an oblique arrow. A – leukocyte α -gal A enzyme activity; L – Lyso-Gb3 level; G – genotype; NC – not checked/refused.

Index patient 2 initially presented with frothy urine, oliguria, facial puffiness, and bilateral pedal edema. Investigations showed proteinuria of 8.45 g/d, and his blood pressure and serum glucose were normal. His renal function gradually deteriorated over 2 years and was subsequently diagnosed as end-stage renal disease of unknown cause. The patient also had intermittent nonspecific headache with 1 episode of generalized tonic-clonic seizure, with computed tomography of the brain showing multifocal infarcts in the background of small vessel ischemia and cerebral atrophy. Electroencephalogram was normal. A screening was done 7 years later when the patient presented to our hospital. He was found to have residual activity of α -gal A with normal lyso-Gb3 level and to carry a novel GLA mutation of c.548-5T>A. Renal biopsy was not done as his kidneys were shrunken, and he had undergone regular dialysis for years. The patient did not have any other manifestations apart from LVH on echocardiogram. Family screening identified another 5 family members who had the same genetic mutation (Figure 2). One of his brothers had chronic neuropathic pain involving bilateral lower extremities. However, he refused any further investigations due to the COVID-19 pandemic. Other family members were asymptomatic.

Discussion

The estimated incidence of FD is about 1 in 117 000 male live births [5]. However, newborn screening initiatives suggest that the incidence may be much higher, ranging from 1: 1500 in Taiwan to 1: 13 341 in Hungary [6,7]. Due to the fact that FD has a wide spectrum of heterogeneously progressive clinical phenotypes, it is likely that many patients, particularly females with FD are undiagnosed [8]. The disease spectrum ranges from the “classic” severe phenotype in males to an asymptomatic disease course observed in females, with a diversity in clinical manifestations between the extremes [9].

The diagnosis of classic FD is easily established in males (hemizygotes) because the enzyme activity is severely reduced or virtually absent in contrast with females (heterozygotes), in whom the enzyme activity in leukocytes may vary considerably in different cell types and tissues [8,9]. There is no clear association between clinical phenotypes and GLA enzyme activity among heterozygous females due to X chromosome inactivation, which may result in expression of α -gal A activity in the plasma or leukocytes within the normal range in up to 60% of women [10]. Thus, due to the overlap in leukocyte α -gal A activities between heterozygotes and noncarriers, mutation screening of GLA via gene sequencing should be part of the molecular genetic work-up in females, whereas enzyme activity measurement is likely adequate for establishing the diagnosis in males [10].

To date, no FD cases have been reported in Malaysia. This study summarized our very first clusters of FD by elucidating the molecular, biochemical, and clinical characteristics of Malaysian FD patients. We believe there are many more patients undiagnosed or unidentified in our nation due to a lack of awareness among clinicians, diversity in phenotypic spectrum, restricted accredited laboratory facilities, and limited resources. Hence, more needs to be done to improve the detection rate of this disorder in Malaysia.

The mechanism by which α -gal A deficiency and glycolipid accumulation result in such a wide variety of complications remains elusive. More than 900 *GLA* mutations have been reported worldwide (Human Gene Mutation Database [HGMD], <http://www.hgmd.cf.ac.uk/>). It is often challenging to clearly determine the relationship between the genotype and phenotype [11].

For index patient 1, a variant within exon 4 of the *GLA* gene (reference sequence: NM_000169.2): c.610 T>C (p.Trp204Arg) was found. This variant, which is classified as likely pathogenic according to the American College of Medical Genetics and Genomics variant classification [12]: PS3 (functional studies) [13,14], has not been reported in the GnomAD database (<https://gnomad.broadinstitute.org/>). To date, only 3 occurrences can be found in ClinVar with no detailed clinical information [14]. To the best of our knowledge, only 1 case report, with a detailed phenotypic description in a female FD patient who carried c.610 T>C variant, was published [15].

Another genetic mutation c.548-5T>A was discovered from our index patient 2. His α -gal A enzyme activity was slightly lower than the lower reference limit and his lyso-Gl3 level was within the reference range. Pedigree analysis revealed nonclassical disease with similar biochemical findings as index patient 2 that may or may not have been caused by FD. To our knowledge, this *GLA* mutation has never been reported in any literature, including HGMD, GnomAD database, and ClinVar. A study reported that an unexpectedly large number of mutations or genetic variants of unknown significance (GVUS) in the *GLA* gene and/or impaired α -gal A activity was found by screening studies in high-risk populations [16]. While the pathogenicity for this mutation is still debatable, we are uncertain whether the mutation of our index patient 2 can be classified under “pathogenic,” “benign,” or “uncertain significance.” Hence, more studies need to be done to confirm the clinical significance of such mutation. The fact that our patient had residual activity of α -gal A is consistent with the GVUS diagnostic criteria as reported in a previous study [16]. Contrary to this, this patient did have end-stage renal failure requiring regular hemodialysis without the evidence of advanced diabetes or hypertension. A renal biopsy, which our patient refused, might be the key determinant to justify the relationship between the

gene mutation and the clinical significance by demonstrating Gb3 accumulation on electron microscopy. In our opinion, the absence of convincing evidence of pathogenicity in our patient with possible GVUS in the *GLA* gene makes the ERT indication less justifiable because its efficacy has not been thoroughly studied [16].

There are several debatable mutations associated with FD, for instance, p.D313Y and intronic variants, p.A143T and p.R112H variants. These have been described in literature as benign by some authors and as pathogenic by others [17,18]. Hence, we should depend on patients' clinical findings, and not only on the genotype, when making a decision whether to commence ERT.

Studies reported that majority of FD patients develop antibodies toward agalsidase ERT, with high prevalence among male patients [19]. This might be attributed to most male FD patients having negligible residual enzyme activity, as was found in our index patient 1. Due to restricted access to laboratory testing and logistic difficulties, it is not feasible to monitor serial antibody titer and lyso-Gb3 levels. This is one of the limiting factors to study the relationship between ERT and the changes in lyso-Gb3 levels in correlation with the clinical outcome. It remains elusive whether long-term efficacy of ERT is hampered by these IgG antibodies and this warrants further studies to answer this hypothesis.

Clinicians should be aware that not all anti-drug antibodies (ADAs) possess neutralizing activity. It is of paramount importance to run neutralization assays to assess the effect of ADAs on clinical and biochemical outcomes [20]. Our index patient 1 showed IgG ADAs with a titer of 3000, but the neutralizing antibody was negative. This finding is consistent with the clinical response, highlighting the fact that ADA-positive status alone is not sufficient to justify the clinically relevant impact of ERT neutralization.

Cardiac involvement is one of the common causes of death in FD in both sexes [21,22], with concentric hypertrophy being the most frequently seen pattern [23]. It leads to progressive concentric, asymmetrical, or apical LVH, with heart failure and arrhythmia as the clinical sequelae. In patients with FD, LV mass and wall thickness increase with age [24]. Having hypertension should not preclude the clinical suspicion of FD, particularly in cases in which the hypertrophy distribution is disproportionate to the severity of hypertension [13,25]. In our study, we detected concentric LVH in 2 index patients who also demonstrated high levels of pro-BNP. Studies have shown that FD patients with elevated pro-BNP had higher risk of progression to cardiomyopathy and heart failure [26,27].

Proteinuria and reduced glomerular filtration rate are reported to be the early renal manifestations in FD patients with the

classic phenotype, and they progressively result in end-stage renal disease in virtually all male patients [28].

It is of paramount importance to detect FD at an early stage and carry out thorough investigations to determine its possibly related comorbidities because it has been shown by recent evidence that the disease progression might be attenuated by early commencement of ERT [28]. For index patient 1, a delay in initiating ERT was due to the challenges posed in reaching the diagnosis and getting the access to treatment in a resource-limited setting. Sophisticated diagnostic assays are not readily available in our nation as local clinicians rarely screen for FD.

The true prevalence of FD in Malaysia is not known. Future systematic screening for the disease, particularly in high-risk population, is warranted, weighing the balance between the clinical benefits of early detection and the potential ethical and psychological ramifications of such a disorder.

Conclusions

This study outlines our local FD landscape and offers objective standards for forward planning. We hope this study may help identify any shortfalls in our health care system, discover areas of concern or potential research, predict future needs, and ensure cost-effective treatment for this group of patients. Shared responsibility among patients, families, care providers, public agencies, nongovernmental organizations, and insurance policy makers should be heightened so as to improve the care of our FD population. A local economic evaluation should be conducted to determine the best model of treatment for FD patients in Malaysia, taking the high diagnostic and treatment cost into consideration.

Ethical Approval

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-20-1752-56072.

Conflicts of Interest

None.

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Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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