A Case Study of Fabry Nephropathy and Its Progression: The First Reported Case in Malaysia

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Abstract

Introduction

Fabry disease (FD) is a rare metabolic disorder caused by the genetic deficiency of the lysosomal hydrolase alpha-galactosidase A, causing common and serious kidney complications. We report the first case of Fabry disease detected in Malaysia.

Clinical Scenario

A 35-year-old man had an incidental finding of proteinuria during routine health screening. His symptoms included frothy urine and intermittent lower limb swelling. Renal biopsy showed features of Fabry's disease which was confirmed with genetic testing. He had classical hemizygous Fabry disease of c.610 C>T with Fabry nephropathy, cardiomyopathy, and cornea verticillata. He was then started on Enzyme Replacement Therapy (ERT) with agalsidase till date.

Conclusion

Proteinuria is the predominant factor in Fabry nephropathy predicting renal disease progression rate. Early Fabry Disease diagnosis could prevent kidney disease progression through the timely initiation of treatment which will help enhance the quality of life of the patient, as the disease progresses.

Background

Fabry Disease (FD) an X-linked lysosomal storage genetic disorder, is caused by deficiency of the α -galactosidase A enzyme (α -Gal A). (1) As a result of the defects in this enzyme, there will be an intralysosomal accumulation of glycosphingolids, particularly globotriosylceramide (GL-3) in different cells, plasma and urine leading to renal, cardiac, and cerebral dysfunction and early death.(2, 3).

The initial proteinuria in the 20s and 30s is among the features of Fabry nephropathy. Among others, there are also features of glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Fabry nephropathy patients may have progressive kidney failure comparable to diabetic nephropathy.(4) Furthermore, Fabry nephropathy is also associated with cardiovascular morbidity and mortality in FD patients.(5) It is estimated that the incidence ranges from 1:40000 to 1:60000 males.(3) The alpha-galactosidase A gene is located on the long arm of chromosome X. Due to its X-linked inheritance, the disease is completely expressed in hemizygous males(3) resulting in the classic form of disease.

Case Presentation

A 35 year old gentleman, who was a non-smoker and teetotaler, complained of intermittent lower limb swelling and frothy urine since 2009. He was normotensive and euglycemic with no known family history of kidney disease. Physical examinations were unremarkable.

Further investigations showed a urine protein dipstick was 2+ with absence of red blood cell or cast under microscopy. His renal profile was normal [initial serum creatinine 63 $\mu\text{mol/l}$, estimated glomerular filtration rate (eGFR) 118 mL/min/1.73m^2 with the CKD-Epi formula)]. 24-hour urine protein was 1.19 g/L with no kidney structural abnormalities being detected by ultrasonography (Right and left kidney sizes measuring 11.3cm and 12.0 cm, respectively). The serum albumin was 39 g/dl with normal total cholesterol level. He was seronegative for syphilis, human immunodeficiency virus (HIV), Hepatitis B and C. Autoimmune screening was negative.

During follow-up, his proteinuria worsened with 24-hour urine protein rising to 2.8 g/L 4 years later. He remained normotensive and euglycemic with no evidence of retinopathy. In view of persistent unexplained proteinuria, renal biopsy (Figure 1) was performed which showed prominent podocytes with expanded abundant cytoplasm that appears pale with fine vacuolation forming lacy appearance. There were also moderate intimal thickening of artery and small foci of tubular atrophy surrounded by interstitial fibrosis seen under microscopy. The immunofluorescence staining for (Ig) G, Ig A, Ig M, (C)3 and C1q were negative. Hence, FD was highly suspected from the overall findings.

Blood sample for Lysosomal Enzymes Assay Test was subsequently sent. Plasma Alpha-galactosidase A (AGAL) Zero nmol/ml/hour (normal reference 2-10). A Genetic study (GLA gene variant Analysis) was conducted based on polymerase chain reaction (PCR) amplification and sequencing methods, confirming the fact that our patient was hemizygous for pathogenic p.Trp204Arg variant (c.610T>C) in the GLA gene, consistent with a final diagnosis of Fabry disease.

Serial system-based physical and ancillary investigations were performed to assess the end-organ involvement of FD. Cornea verticillate were noted in both eyes via slit-lamp examination. Transthoracic echocardiogram showed moderate concentric left ventricular hypertrophy (LVH) with LV ejection fraction above 55%. The other organ systems, including neurology, cutaneous, ears, gastrointestinal tract, cerebrovascular and psychology were unremarkable. Hence, a final diagnosis of FD with renal, ocular, and cardiovascular was made.

He was then commenced on ERT - intravenous Fabrazyme 35 mg two weekly for first two doses, followed by the maintenance regimen 70 mg (1mg/kg) every 2 weeks five years after the FD diagnosis was made and almost a decade after his initial presentation. He was also started on low dose Perindopril (a type of angiotensin-converting enzyme ACE inhibitor) for his proteinuria. He remained on these treatments with normal blood pressure to date (approximately two years post ERT commencement). The serial investigation was shown in Table 1.

Table 1: Serial investigation during period of follow-up

	At presentation (2009)	During renal biopsy (Dec 2013)	At initiation of treatment (Dec 2018)	At 1 year after treatment (Dec 2019)	At present (Aug 2020)
24-hour Urine protein (g/L)	1.19	2.8	2.51	2.46	3.15
Serum creatinine (umol/L)	63	74	118	164	178
eGFR mL/min/1.73 m ² (CKD-epi formula)	113	110.5	64.3	42.9	38.6

His proteinuria showed no improvement despite starting on ERT and kidney function also showed deterioration of 4.3ml/min/1.73m² per year. However, extrarenal manifestation, cardiomyopathy showed improvement, whereby, repeated echocardiogram in 2019, showed normal left ventricular cavity size and normal wall thickness.

He has 2 younger brothers and 1 younger sister. Enzyme and genetic studies were performed for the siblings using Dry Blood Spot with capillary blood. His younger sister was detected to have FD through the screening with heterozygous mutation of p.Trp204Arg. His mother was also found to have similar mutation.

He has 5 children: 1 son and 4 daughters. His son was tested but was found to be healthy. However, 4 of his daughters were detected to have heterozygous mutation for p.Trp204Arg. This is illustrated in the Figure 2.

Discussion

Fabry nephropathy is common in Fabry's disease. Typically, Fabry nephropathy is known and likely to start at a young age. Renal biopsies of children and adolescent who had normal eGFR and no proteinuria had exhibited glomerular sclerosis and vascular lesions;(6, 7) and glomerular GL-3 have also been detected in foetuses.(8) Our patient had a more severe form of nephropathy where his a-galactosidase levels is 0% and overt proteinuria at an early age. This is explained by Mahmud *et al.*, where patients with a-galactosidase levels of less than 1% tends to be more severe. Those with enzyme level detectable the renal involvement is usually less severe and begins late at a mean age of 47 years.(9)

To date more than 900 mutations of agalactosidase gene have been recorded in human mutation database.(10) Most families have private mutations which may explain the variations in clinical presentation of Fabry's disease. The variant both our patient and his family have is a rare heterogenous

variant of c.610T > C. To date, only 3 occurrences can be found in ClinVar with no detailed clinical information.(11)

In renal biopsy, a typical histopathological lesion is the diagnostic of Fabry Disease. Here Fabry's inclusions can be identified with PAS or Papanicolaou stain demonstrating vacuolated epithelial cells on light microscopy and Maltese cross pattern under polarized light or characteristic lamellar pattern on electron microscopy. (9) This is as shown in the renal biopsy of our patient which showed the all the typical features.

The mainstay of treatment of FD is ERT, and its initiation is recommended in classically affected males and females as soon as early clinical signs of FD occurrence.(12)

For normal population as well as for FD patients, it is a known fact that kidney function decreases with age.(2, 3) Nowak *et al.* found that male FD patients showed a clear decline of kidney function (eGFR) of 3.07 ml/min/1.73m² per year over time despite being on ERT. It has also been proposed that male FD patients can pass through several CKD stages ending up with end-stage renal disease within 15 years after the initiation of ERT later in the stage. They also observed that the late initiation of ERT, does not show clear treatment-related benefit on the development of Fabry nephropathy.(13) Our patient was initiated ERT at the age after 35 which is considered late stage and already had significant proteinuria. There are no changes seen in the proteinuria over the years. He had rapid declination in renal function compared to normal population about 4.3ml/min/1.73m² per year but slower declination compared to untreated male FD. Schiffmann *et al.*, reported that for untreated male FD with substantial proteinuria, the rates of renal declination is 6.9 ml/min/1.73 m² per year(14) while Branton *et al* reported a declination rate of 12 ml/min/1.73 m² per year.(15)

On the other hand, recent study has found that proteinuria seems to be associated with decreased effectiveness of ERT.(16, 17) According to Nowak *et al.*, disease progression was accelerated if ERT patients already had a more severe albuminuria at baseline, similar to this case.(13) This is supported by Wanner C *et al.* in which their studies showed that patients with faster progression had significantly higher proteinuria and renal function and men declined more rapidly for those with increased urinary protein levels.(18) However, studies suggest that maximal treatment effect in Fabry nephropathy can be achieved at an early stage with normal or almost normal kidney function.(19, 20) This maximal treatment also proved to provide better renal and cardiovascular outcome.(20) ACEi/ARB therapy in conjunction with ERT can reduce proteinuria and stabilize renal function in Fabry patients.(21) Similarly, in this case Perindopril was started for this reason.

In addition to that, another possibility for poor treatment response is the development of neutralizing antibody to ERT. In a study conducted by Linthorst *et al.*, it was found that 69% of male FD developed Ig G antibodies to [agalsidase alpha and beta](#) within 6 months of treatment especially in patient who does not express residual enzyme activity, similar to our patient.(22) And it was also found that once neutralizing antibody had developed, it is irreversible and would stay positive for over 10 years.(23) However, due to

restricted local resources, the Ig G antibodies development towards agalsidase beta in the patient was not able to be confirmed. Furthermore, there is no alternative treatment which is currently available for classic male FD with lack of enzyme activity.

Despite the progression of Fabry nephropathy, the treatment of ERT had not been stopped as it was not recommended to stop even in severe renal insufficiency (GFR < 45 ml/min/1.73 m²) or those on dialysis or with cognitive decline. It was however carefully considered on an individual basis.(12) As once GFR has been compromised, the goal is reduction and stabilization in the rate of CKD progresses.(24) Furthermore, ERT can reduce the occurrence of major renal, cardiac, and cerebrovascular events. Further reported extra-renal benefits include, for example, decrease in neuropathic pain, improvement of gastrointestinal symptoms, and reduction of left ventricular mass.(4)

Conclusion

To conclude, Fabry Disease is a rare disease with wide spectrum of clinical manifestations which makes the diagnosing even more difficult for clinicians. Thus, in cases where no apparent causes can be found, high index of suspicion is the key. Proteinuria is the predominant factor in Fabry nephropathy predicting renal disease progression rate. Therefore, an early Fabry Disease diagnosis could prevent kidney disease progression through the timely initiation of treatment which will help enhance the quality of life of the patient, as the disease progresses.

Learning points

- Fabry Disease is a rare disease with wide spectrum of clinical manifestations
- High index of suspicion in cases where no apparent causes can be found
- Early diagnosis is needed for timely initiation of ERT to enhance quality of life of the patient

Declarations

Ethical Approval and consent to participate

This article does contain studies with human participant and was registered via National Medical Research Register, Ministry of Health Malaysia with a registered ID of NMRR-20-1356-55632

Consent for publication

Written informed consent was obtained from all participants included in the case report

Conflict of Interest

The authors declare no competing interests

Funding

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Author's contribution

IPLT was responsible for the study design, data collection, manuscript writing, ASOT, participated in data collection and contributed to case illustration and discussion. TLF and CHHT were involved in the manuscript editing and language proofreading. All authors read and approved the final manuscript.

Availability of Data and Materials

The data that support the findings of this study are available from Medical Records Unit, Miri Hospital but restrictions apply to the availability of these data, which were used under special written permission and consent of patients for the current case report, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Medical Records Unit, Miri Hospital and Ministry of Health, Malaysia.

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Figures

Figure 1

Renal biopsy showing prominent podocytes with abundant foamy cytoplasm

Figure 2

Family tree