Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Case Report
Volume 20 Issue 5 - August 2024
DOI: 10.19080/ARGH.2024.20.556047

Adv Res Gastroentero Hepatol

Fabry Disease: The Worst Possible Outcome?

Gustavo Cabrera[1]*, Fernando Perretta[2]*, Pablo Bevione[2], Valeria Alberton[3], María Sol Meregone[4] and Juan Politei[5]

[1]*Santa María de la Salud, San Isidro, Provincia de Buenos Aires, Argentina*

[2]*NEFRA Medical Care Pilar, Pilar, Provincia de Buenos Aires, Argentina*

[3]*Hospital Fernández, CABA, Argentina*

[4]*Hospital Sanguinetti, Pilar, Provincia de Buenos Aires, Argentina*

[5]*Fundación SPINE, CABA, Argentina*

Submission: August 14, 2024; **Published:** September 5, 2024

Corresponding author: Dr. Fernando Perretta, Edilfredo Ameghino 345, B1625, Escobar, Provincia de Buenos Aires, Argentina

*These two authors are equal contributors to this work and designated as co-first authors.

Abstract

Fabry disease (FD) is a metabolic storage disorder which causes progressive accumulation of glycosphingolipids and cellular dysfunction. Neurological, cardiac, and renal compromise significantly reduces life expectancy. Gastrointestinal signs and symptoms, including abdominal pain, nausea, diarrhea and diverticular disease, are frequent reported complaints in patients with FD. Intestinal dysmotility as well as impaired autonomic function, vasculopathy and myopathy are the responsible of these enteric symptoms. In few patients, colonic dysmotility due glycolipid accumulation in autonomic plexus and ganglia can lead to pseudo-obstruction syndrome with intestinal ischemia and necrosis. Different studies have reported that enzyme replacement therapy (ERT) improve gastrointestinal manifestations. An early treatment in asymptomatic or oligosymptomatic Fabry patients may be justified to prevent the progression of the disease. A case of a severe gastrointestinal involvement in a classic male adult patient on ERT, with a late FD diagnosis, is reported.

Keywords: Fabry Disease; α-Galactosidase A; Globotriaosylceramide; Gastrointestinal Involvement

Abbreviations: FD: Fabry Disease; ERT: Enzyme Replacement Therapy; MRI: Magnetic Resonance Imaging; GFR: Glomerular Filtration Rate; ESRD: End-Stage Renal Disease; WML: White Matter Lesions

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by a deficiency of the α-galactosidase A enzyme (α-GalA). The result is the accumulation of globotriaosylceramide (GL-3 or Gb3) and related glycosphingolipids. Clinical manifestations, such as angiokeratoma, gastrointestinal symptoms, corneal dystrophy and acroparesthesias, often begin in childhood and adolescence in the classic phenotype [1]. Renal impairment, cerebrovascular complications and cardiac manifestations usually occur in adulthood. The cardiovascular manifestations are crucial for patients' morbidity and mortality [2]. Gastrointestinal signs and symptoms -abdominal pain, nausea, diarrhea, and diverticular disease- are some of the most frequently reported complaints in patients with FD since childhood. In some cases, chronic intestinal pseudo-obstruction results in clinical manifestations that resemble bowel obstruction and requires a colostomy [3,4].

Over the past 22 years, the prognosis of FD has changed due to the availability of enzyme replacement therapy (ERT). An analysis of the Fabry Outcome Survey database showed that ERT reduced the prevalence of gastrointestinal signs and symptoms in FD, especially in children and male patients, after 12 and 24 months of treatment [5]. Banikazemi et al. reported four adult male patients with severe gastrointestinal symptoms who participated in clinical trials of ERT with agalsidase beta; after 6-7 months a reduction in abdominal pain or diarrhea was observed, the patients discontinued their gastrointestinal medications, and gained 3-8 kg [6]. Gastrointestinal compromise in FD is often misdiagnosed or under-reported. This case report describes a severe gastrointestinal involvement in a classic male adult patient on ERT with a late FD diagnosis.

Case Report

A 37-year-old Caucasian man on hemodialysis for the last two years attended to the ultrasound department for a control of his arteriovenous fistula. During the procedure, we realized his acromegalic face and some skin lesions in abdomen that

resembled angiokeratomas. Medical history revealed other symptoms that included chronic abdominal pain and episodes of diarrhea during childhood, intermittent neuropathic pain in the hands and feet, and hypohidrosis. All these features made us suspect that the patient could suffer from FD. The dosage of α-GalA activity in dry blood spot was 0.1 nmol/h/L, which was below normal ranges (reference value ≥ 4.0), and a molecular genetic analysis confirmed the diagnosis. The variant of the GLA gen was c.1244T>C (p.L415P), a missense mutation related to classic phenotype. The echocardiogram evidenced a severe concentric hypertrophy with a left ventricular mass index of 193 gr/m^2 and a normal ejection fraction (EF: 66%). The patient did not report chest pain, dyspnea, or palpitations.

Few weeks after diagnosis, ERT with agalsidase beta at doses of 1 mg/kg body weight every other week by intravenous infusion during dialysis was initiated, with good tolerance and without adverse effects. A year later, sudden deafness appeared in both ears without response to steroid treatment. After that episode, the patient was hospitalized because of a transient ischemic attack with speech disturbance and right arm paresis. A brain magnetic resonance imaging (MRI) showed an increase in the number of white matter lesions in comparison to the former MRI done 2 years before. At the age of 39, the patient developed fever and progressive left lower-quadrant abdominal pain. After 3 days of conservative treatment, physical exam revealed severe abdominal distention, with food intolerance, and increasing pain, which required urgent surgery. Figure 1 shows the standing abdominal x-ray with severe colonic distension. A Hartmann's procedure was performed, resection of the rectosigmoid colon with closure of the anorectal stump and formation of an end colostomy. Few days later, the patient presented necrosis of colostomy with sepsis and multiple organ dysfunction syndrome, dying in the intensive care unit. Histological results showed enlarged and vacuolated ganglion cells in the Meissner's and Auerbach's plexuses (Figure 2); intracellular inclusions in smooth muscle cells of small arteries walls (Figure 3); foamy macrophage in the mucosa between glands, and in the sinus of lymph nodes (Figure 4). There was also noted the presence of foci of ulceration and superficial necrosis of the mucosa (Figure 5).

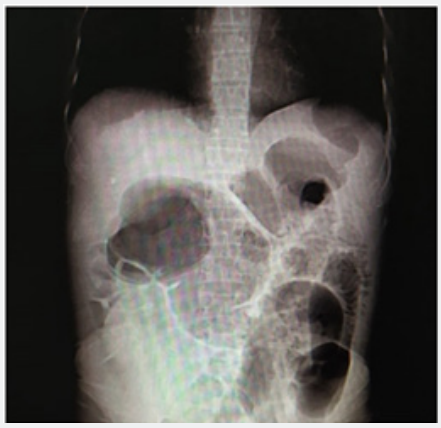

Figure 1: Standing abdominal x-ray.

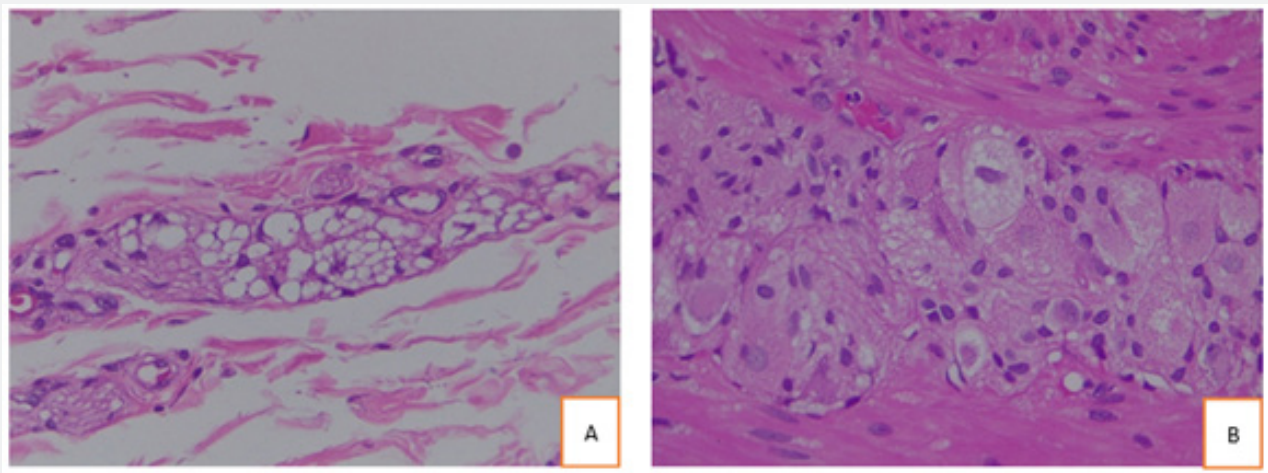

Figure 2: Hematoxylin-Eosin (H&E). A: 40X; B: 200X. Vacuolated cytoplasm of submucosal and myenteric plexus colon cells. Ganglion cells appear markedly foamy.

How to cite this article: Cabrera G, Perretta F, Bevione P, Alberton V, Meregone MS, et al. Fabry Disease: The Worst Possible Outcome?. Adv Res Gastroentero Hepatol, 2024; 20(5): 556047. DOI: 10.19080/ARGH.2024.20.556047

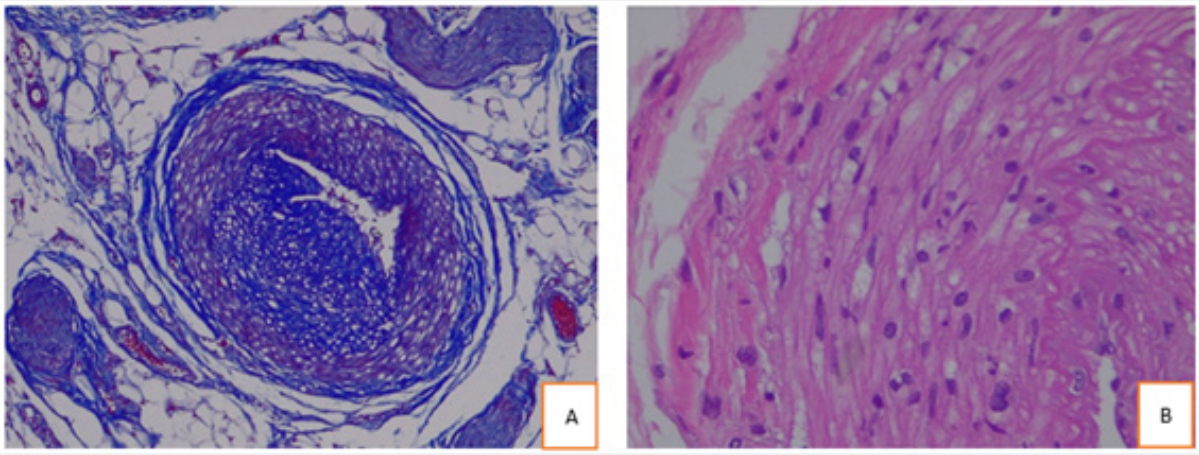

Figure 3: A: Masson Trichrome stain 40X: narrowing of vascular lumen; B: H&E 200X: presence of vacuolated smooth muscle and intimal cells of submucosal arteries.

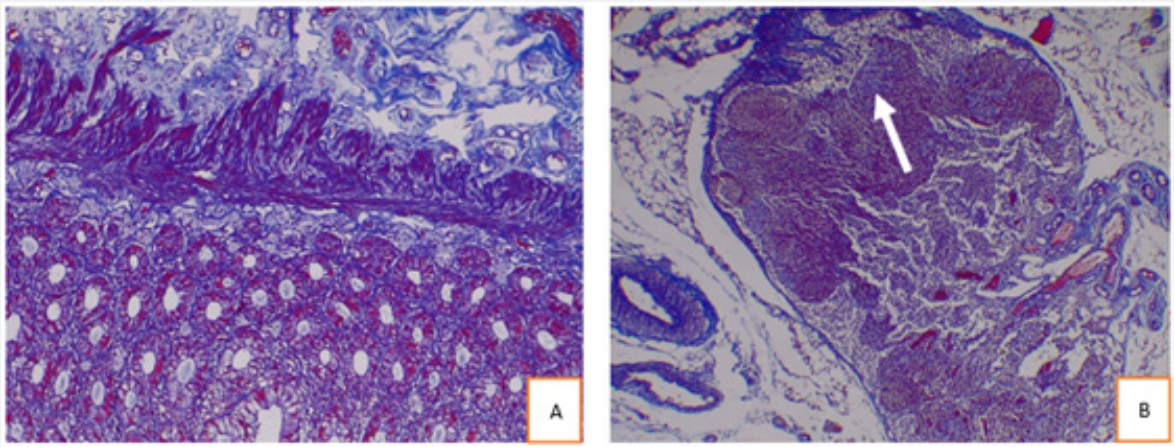

Figure 4: A: Masson Trichrome stain 40X: presence of foamy macrophage cells between the glands in the colonic mucosa; B: and in the sinus of a lymph node (white arrow).

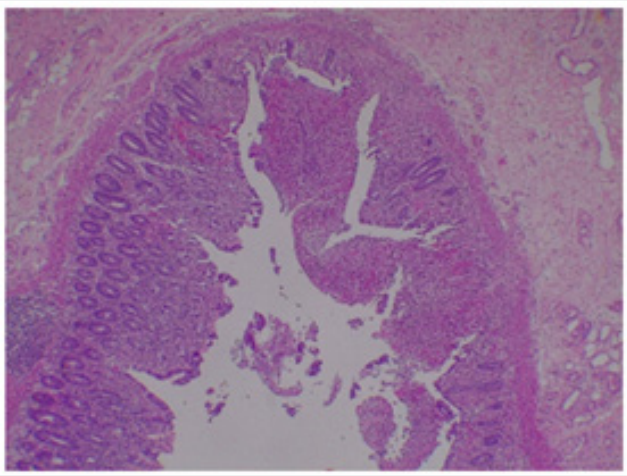

Figure 5: H&E 40X: foci of ulceration and superficial necrosis of the colonic mucosa.

How to cite this article: Cabrera G, Perretta F, Bevione P, Alberton V, Meregone MS, et al. Fabry Disease: The Worst Possible Outcome?. Adv Res Gastroentero Hepatol, 2024; 20(5): 556047. DOI: 10.19080/ARGH.2024.20.556047

Discussion

We report a case of a 37-year-old man with FD on dialysis that suffered many adverse events after 2 years of ERT. The cause of his death was an intestinal pseudo-obstruction, and complications after Hartmann's surgery. Abdominal pain, nausea, diarrhea, and diverticular disease are some of the most frequent gastrointestinal signs and symptoms reported in patients with classic FD. These symptoms are due to intestinal dysmotility as well as impaired autonomic function, vasculopathy and myopathy. Several studies have demonstrated that ERT alleviates gastrointestinal manifestations. In some cases, chronic intestinal pseudo-obstruction resembles a typical intestinal obstruction in which an unnecessary colostomy is performed [3,4]. Nephropathy is one of the major complications of FD. Renal biopsies revealed GL-3 accumulation in almost all kidney cell types, with focal and global glomerulosclerosis as early as in the second decade of life. The major signs of Fabry nephropathy include reduced glomerular filtration rate (GFR), isosthenuria and proteinuria, more frequently affects male patients, and typically progress to end-stage renal disease (ESRD) by age thirty or forty [7,8,9,10]. Proteinuria and progressive renal failure may develop rapidly in FD. Schiffmann et al. re-examined the natural history of Fabry nephropathy with a retrospective analysis of 279 men and 168 women. In men with an estimated GFR of more than 60 ml/min/1.73 m^2, the slope of renal function was -3 and for women was -0.9 ml/min/1.73 m^2 per year; for men with an estimated GFR <60 ml/min/1.73 m^2, it was -6.8 and for women it was -2.1 ml/min/1.73m^2 per year.

Patients with reduced estimated GFR and/or proteinuria ≥1 g/24 h had a worse prognosis [11]. Our patient was on dialysis for the last two years with an unknown etiology of his renal disease. Because a significant number of patients with FD progress to ESRD, screening in the dialysis population is a useful tool to identify new cases [12]. A review of screening carried out in patients on dialysis that included a total of 7,182 male and 4,179 female showed a mean prevalence of 0.33% and 0.10% respectively [13]. In Argentina the prevalence rate of FD in male dialysis patients was 0.23%; classic phenotype was observed in 73%, whereas the remaining 27% presented as late-onset variant [14]. Agalsidase beta, a form of recombinant human α -GalA, was approved for use as ERT for FD. In clinical studies, agalsidase beta removed microvascular endothelial GL-3 deposits from kidney, heart and skin cells. It also provided long-term stabilization of renal function in patients with mild renal involvement and delayed time to renal, cardio, and cerebrovascular events in patients with advanced FD. ERT did not stabilize renal function in patients with severe renal impairment (proteinuria ≥1 g/24 h or estimated GFR <60 ml/min/1.73 m^2) [15,16]. In this case, the patient started ERT on dialysis. There are limited available data about FD patients receiving ERT and undergoing dialysis at the same time. In an open-label nonrandomized Italian study that enrolled 9 FD patients on dialysis, after 2 years of ERT an overall amelioration of clinical symptoms was observed; pain crises disappeared completely after approximately 6 months, and gastrointestinal involvement improved after 6 to 8 months of treatment [17]. Mignani et al. conducted a nationwide survey in Italy to elucidate the cardiac status and renal allograft function in FD patients on renal replacement therapy and ERT. Cardiac parameters increased in dialysis group, but in transplant patients seemed to stabilize. Reduction in renal allograft function was mild (-1.92 ml/min/year), and severe events occurred more frequently in the dialysis group. They concluded that kidney transplantation should be an option for FD patients progressing to ESRD [18].

A retrospective cohort study in Argentina about vascular disease in male patients with FD on hemodialysis was performed; 50% of patients presented a severe vascular event in an average time of 38 months approximately since admission to dialysis [19]. In patients on dialysis stroke is the third most common cause of cardiovascular disease death. In a prospective national cohort study, the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study 1,041 incident dialysis patients were enrolled from October 1995 to July 1998, followed up until December 31, 2004. One hundred sixty-five participants experienced a cerebrovascular event with an overall incidence of 4.9 events/100 person-years. Ischemic stroke was the most prevalent, with a 76% of all 200 events. The authors concluded that cerebrovascular disease is frequent in patients undergoing dialysis, late identified, and carries a significant risk of morbidity and mortality [20]. Before starting ERT, our patient showed multiple and confluent white matter lesions (WML) in brain magnetic resonance images. Ischemic stroke and transient ischemic attacks are the most prevalent cerebrovascular events in FD patients and occur at an earlier age than the general population. The images found in our patient were considered characteristic neuroradiological signs of FD. Microvascular degeneration because of GL-3-related endothelial damage can lead to injury and appears as abnormal hyperintensities in brain parenchyma.

These WML occur in the subcortical, deep, and periventricular region, usually in a symmetrical manner, and have been shown to increase in number with age progression [21]. A higher WML load may be an indicator of progressive cerebrovascular disease in Fabry patients as we observed in this case. Fellgiebel et al. reported that ERT can reduce the progression of cerebrovascular disease, even in advanced FD patients, suggesting that an early treatment could stabilize WML progression and the risk of stroke, but in this cohort patients on dialysis were excluded [22]. In our local experience, no change in existing ischemic brain lesions and no new brain lesions were seen in 6 patients on ERT with agalsidase beta followed for 10 years [23]. Better results may be observed when treatment is started at an early age prior to the development of irreversible organ damage such as chronic kidney disease, WML or cardiac fibrosis. In this case the diagnosis was delayed for almost 30 years, even after starting dialysis the delay was 2 years. To date, ERT efficacy in reducing cardiac and cerebrovascular mortality in patients with ESRD undergoing dialysis has not been shown.

How to cite this article: Cabrera G, Perretta F, Bevione P, Alberton V, Meregone MS, et al. Fabry Disease: The Worst Possible Outcome?. Adv Res Gastroentero Hepatol, 2024; 20(5): 556047. DOI: 10.19080/ARGH.2024.20.556047

Regarding ERT effect over gastrointestinal involvement, there are few publications that reported reduction in symptoms, but none shows reduction in vascular involvement or prevention of ischemia and/or intestinal pseudo-obstructions. Gastrointestinal compromise in Fabry patients is often misdiagnosed or under-reported, and in certain patients, it could be so severe as to cause serious morbidity even death, as in this case report.

References

1. Desnick RJ, Brady R, Barranger J (2003) Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 138(4): 338-346.
2. Breunig F, Weidemann F, Beer M (2003) Fabry disease: diagnosis and treatment. Kidney Int Suppl (84): S181-S185.
3. Politei J, Thurberg BL, Wallace E (2016) Gastrointestinal involvement in Fabry disease. So important, yet often neglected. Clin Genet 89(1): 5-9.
4. Politei J, Durand C, Schenone AB, Torres A, Mukdsi J, et al. (2017) Chronic intestinal pseudo-obstruction. Did you search for lysosomal storage diseases? Mol Genet Metab Rep 11: 8-11.
5. Hoffmann B, Schwarz M, Mehta A, Keshav S (2007) Fabry Outcome Survey European Investigators. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol 5(12): 1447-1453.
6. Banikazemi M, Ullman T, Desnick RJ (2005) Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. Mol Genet Metab 85(4): 255-259.
7. Grünfeld JP, Lidove O, Joly D, Barbey F (2001) Renal disease in Fabry patients. J Inherit Metab Dis 2: 71-65.
8. Thurberg BL, Rennke H, Colvin R (2002) Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int 62(6): 1933-1946.
9. Tøndel C, Bostad L, Hirth A, Svarstad E (2008) Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. Am J Kidney Dis 51(5): 767-776.
10. Jaurretche S, Antogiovanni N, Perretta F (2017) Prevalence of chronic kidney disease in fabry disease patients: Multicenter cross sectional study in Argentina. Mol Genet Metab Rep 12: 41-43.
11. Schiffmann R, Warnock DG, Banikazemi M (2009) Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 24(7): 2102-2111.
12. Perretta F, Antongiovanni N, Jaurretche S (2018) Fabry Disease: Why suspect it in patients on dialysis? JOJ uro & nephron 5(2): 555-656.
13. Linthorst GE, Bouwman MG, Wijburg FA, Aerts JM, Poorthuis BJ, et al. (2010) Screening for Fabry disease in high-risk populations: a systematic review. J Med Genet 47(4): 217-222.
14. Frabasil J, Durand C, Sokn S (2019) Prevalence of Fabry disease in male dialysis patients: Argentinean screening study. JIMD Rep 48(1):45-52.
15. Warnock DG, Ortiz A, Mauer M (2012) Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant 27(3): 1042-1049.
16. Cabrera G, Politei J, Antongiovani N, Amartino H (2017) Effectiveness of enzyme replacement therapy in Fabry disease: Long term experience in Argentina. Mol Genet Metab Rep 11: 65-68.
17. Pisani A, Spinelli L, Sabbatini M (2005) Enzyme replacement therapy in Fabry disease patients undergoing dialysis: effects on quality of life and organ involvement. Am J Kidney Dis 46(1): 120-127.
18. Mignani R, Feriozzi S, Pisani A (2008) Agalsidase therapy in patients with Fabry disease on renal replacement therapy: a nationwide study in Italy. Nephrol Dial Transplant 23(5): 1628-1635.
19. Jaurretche S, Antongiovanni N, Perretta F Enfermedad vascular en pacientes varones con enfermedad de Fabry en hemodiálisis: estudio de cohorte retrospectivo en Argentina. Rev Nefrol Dial Traspl.
20. Sozio SM, Armstrong PA, Coresh J (2009) Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis 54(3): 468-477.
21. Kolodny E, Fellgiebel A, Hilz MJ (2015) Cerebrovascular involvement in Fabry disease: current status of knowledge. Stroke 46(1): 302-313.
22. Fellgiebel A, Gartenschläger M, Wildberger K, Scheurich A, Desnick RJ, et al. (2014) Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis 38(6): 448-456.
23. Juan P, Hernan A, Beatriz SA (2014) Fabry disease: multidisciplinary evaluation after 10 years of treatment with agalsidase Beta. JIMD Rep 16: 7-14.

DOI: 10.19080/ARGH.2024.20.556047

How to cite this article: Cabrera G, Perretta F, Bevione P, Alberton V, Meregone MS, et al. Fabry Disease: The Worst Possible Outcome?. Adv Res Gastroentero Hepatol, 2024; 20(5): 556047. DOI: 10.19080/ARGH.2024.20.556047