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CASE REPORT OF LATE ONSET FABRY DISEASE WITH TYPICAL PRESENTATION

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ABSTRACT

Fabry disease is a lysosomal lipid storage disorder which can affect multiple organs especially heart, kidney and brain. Enzyme replacement therapy is the main mode of treatment available which will be effective only when initiated at an early stage. So early diagnosis and early initiation of treatment is essential to improve the quality of life of the patient. This is a case of late onset Fabry disease with typical symptoms started at 23 years with angiokeratoma lesions whose diagnosis was delayed and hence initiation of enzyme replacement therapy was also delayed. In spite of taking regular enzyme replacement therapy after diagnosis, patient developed end stage renal disease. This shows the importance of development of proper screening methods for early diagnosis of Fabry disease, so that initiation of treatment can be done at an early stage which is likely to prevent or reduce complications.

INTRODUCTION

Sphingolipidoses are lysosomal lipid storage disorders characterized by deficiency of enzymes required for degradation of sphingolipids. Fabry disease is the only X linked recessive sphingolipidosis. Global prevalence estimates of Fabry disease based on clinical ascertainment range from 1 in 40,000 to 1 in 1,70,000.(1) It is characterized by deficiency of enzyme α-Galactosidase due to mutation in GLA (alpha galactosidase A) gene. The conversion of globotriaosylceramide(Gb3) to lactosylceramide is affected leading to the accumulation of Gb3.The progressive accumulation of Gb3 can lead to organ damage mostly in the heart, kidney, and brain.(2)Fabry disease has two recognized forms. The classic type with little or no residual alpha galactosidase activity appears in childhood and is severe.(2)Late-onset Fabry disease generally manifests after age of 30 years and has some residual alpha galactosidase activity (3-15 percent of normal), and presents with milder symptoms.(2)

CASE HISTORY

A 44 year old male patient was admitted in nephrology ward due to renal failure and was started on dialysis. History revealed symptomatology started at age of 23 years when he developed angiokeratoma mainly on abdomen and sparsely on limbs for which the patient did not seek treatment and no evaluation was done. At 37 years he was admitted in hospital with cerebrovascular accident(CVA)-right sided hemiparesis.On examination blood pressure was high. Laboratory investigations showed normal results except serum creatinine- 1.5 mg/dl and 24 hour urine protein -860 mg/24 hours. Patient was put on antihypertensives. During his follow up progressive renal disease was found. Renal biopsy was done which showed glomerulosclerosis, vacuolated cells,thickened

vessel wall. Ophthalmology evaluation was done and patient was found to have corneal opacity but no ocular symptoms. Past history of angiokeratoma, CVA, renal biopsy findings and continuous rise in renal parameters led to suspicion of Fabry disease. As per family history, elder brother died of CVA at 43 years and elder sister is alive and healthy with lesions of angiokeratoma. Based on symptoms of patient and family history, enzyme assay and genetic analysis was done. Alpha Galactosidase enzyme assay showed reduced activity and GLA gene mutation analysis was positive.

With confirmed diagnosis patient was put on enzyme replacement therapy with recombinant alpha galactosidase A and was discharged with advice to follow up. At the age of 44 years patient presented with end stage renal disease with secondary hyperparathyroidism and was put on hemodialysis. Cardiology evaluation was done at 44 years.2D echocardiography showed concentric left ventricular hypertrophy, moderate to severe aortic regurgitation and moderate mitral regurgitation. End stage renal disease has developed complication of secondary hyperparathyroidism. On examination, angiokeratoma lesions are present mainly on abdominal region.

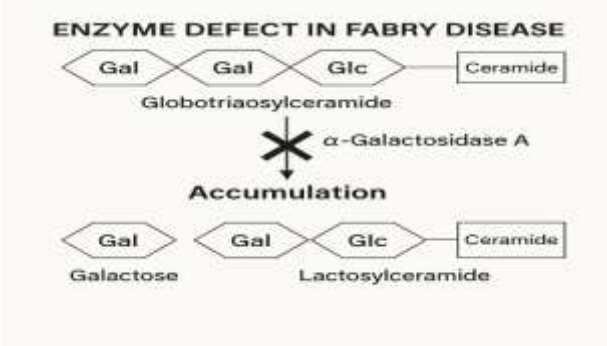

Fig 01: Enzyme defects in Fabry Disease.

INVESTIGATIONS

Urea	58.9(15-40mg/dl
Creatinine	7.38(0.7-1.4mg/dl)
Sodium	140.5 (136-145mEq/L)
Potassium	4.70(3.5-5mEq/L)
Chloride	102.2(96-106mEq/L)
RBS	81mg/dl
Vitamin D	9.29(30-100ng/ml)
ALP	308.27(40-125U/L)
Calcium	7.9(9-11mg/dl)
iPTH	253.5(14-72pg/ml)

Alpha-galactosidase A activity - significantly reduced, GLA gene mutation – positive

DISCUSSION

The patient is the third male child of third degree consanguineous marriage. Elder brother died at the age of 43 years due to complications of cerebrovascular accident probably due to Fabry's disease but diagnostic tests were not performed.Elder sister is carrier with angiokeratoma lesions.Younger brother is asymptomatic but GLA gene mutation analysis is positive.Patient's daughter is also carrier. Patient's first symptom of angiokeratoma at 23 years was ignored when vascular complications might have started which led to CVA and progressive renal disease. This is a case where enzyme replacement therapy was not effective.Hypothetically there can be two reasons: Not starting the therapy at the right time as it was not diagnosed at the right time (at the onset of angiokeratoma lesions, it was ignored). In spite of starting enzyme replacement therapy after onset of CVA and mild kidney involvement, deterioration of patient might be due to occurrence of neutralizing antibodies or decrease in uptake of the enzyme.(3) Treatment with recombinant α-galactosidase A clears microvascular endothelial deposits of globotriaosyl ceramide from the kidneys, heart, and skin.(3) In patients with advanced organ involvement including chronic kidney disease, progression of disease occurs despite enzyme replacement therapy.(3) Initiation of enzyme replacement therapy at an early stage can either prevent or delay the

occurrence of complications and improve the quality of life of patient.(4) New modalities of treatment under study include Chaperone therapy, second generation enzyme replacement therapies, substrate reduction therapies, mRNA and gene based therapy. (5)
The economical and social burden on our society by congenital disorders is enormous. Fabry disease is one such congenital disorder for which proper screening methods is not available. Efforts should be made for effectively screening the population for Fabry disease so that diagnosis and initiation of treatment is not delayed.

CONCLUSION

This case highlights the progressive nature and multisystem involvement of Fabry disease, a rare X-linked lysosomal storage disorder, which often remains undiagnosed or misdiagnosed until irreversible organ damage occurs. The patient presented with classic early signs-angiokeratoma and hypertension-but due to lack of early recognition and screening, he later developed cerebrovascular complications, progressive renal failure, and cardiac involvement, culminating in end-stage renal disease (ESRD).

Declaration: The data for this study was collected in compliance with ethical standards. This study received no specific grant from any funding agency, and the authors declare that they have no conflict of interest.

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