P.G35V: A NEW MUTATION, EARLY RENAL MANIFESTATIONS IN FABRY DISEASE

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INTRODUCTION

Fabry disease (FD) is an X-linked genetic disease that causes cellular accumulation of globotrialosilceramida (Gb3) due to lack of lisossomal activity of alpha galactosidase A (alpha-gal A) enzyme. Kidney involvement is variable and common. It starts with deposition of Gb3 in every kidney cell causing proteinuria and progressive renal loss. Men classically develop chronic kidney disease that needs renal replacement therapy and women can present with different stages of severity. The enzymatic replacement therapy could delay the progression of chronic kidney disease and improve quality of life.

CASE PRESENTATION

RMO, male, 43 years old, with chronic kidney disease in replacement therapy of unknown cause since he was 35 years old; presenting typical manifestations of FD. Enzymatic tests were done and detected low activitiy of alpha-GAL enzyme. Genotype confirmed the mutation p.G35V in homozygosity in exon 1, not already described in literature and with unknown clinical effect. By mutation analysis by Polyphen-2 software (available at http://genetics.bwh.harvard.edu/pph2), the pathogenic potential of the mutation was confirmed. The index patient started enzymatic replacement therapy with human recombinant alpha-Gal A enzyme (Fabrazyme®). Family screening was done and 11 first, second and third-degree relatives had the mutation (tabel 1). One of the nephews of the index patient, 27 years old, presented severe neurologic symptoms, such as multiple strokes and movement loss. Five of the mutation carriers (2 sisters and 3 nephews) presented with proteinuria between 150 and 1000mg/24hours and underwent kidney biopsy. The electron microscopy showed foot-process effacement and amellated membrane inclusion bodies in podocytes, which are the hallmark of the disease, and either “zebroid” and “myelin – like” appearance in endothelial cells (tabel 2). In addition, there is evidence of cardiologic involvement in 4 of these patients (short PR interval or left ventricular hipertrophy).

DISCUSSION

This case report illustrates the genetic inheritance of FD and its new mutation, not already described in medical literature. It has different characteristics and different stricken organs in the same family members. At the same time, is observed the predominance of kidney involvement in most of them. Even patients with normal serum creatinine present multiple histopathological findings of the underlying disease. In addition to enzymatic replacement therapy, it is indicated the use of angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors to control proteinuria and slow the progression of chronic kidney disease.

CONCLUSIONS

Doctors should be familiarized with signs and symptoms of FD and consider this pathology as a differential diagnosis once the delay in diagnose can lead to irreversible organ damage and reduce the efficacy of the specific treatment.

REFERENCES

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Tabel 1: Clinical, laboratorial and echocardiographic findings in patients with Fabry disease. GFR: Glomerular Filtration Rate. CKD: Chronic Kidney Disease

	Male,43y Index	Male,27y Nephew	Male,25y Nephew	Female, 49y Sister	Female, 49y Sister	Female,47y Sister	Female,30y Niece	Female, 27y Niece	Female, 22y Daughter	Female,16y Daughter
Creatinine (mg/dL)	7,6	0,7	0,98	0,7	0,9	0,9	0,9	0,7	0,8	0,9
GFR (mL/min) CKD-EPI equation	On Dialysis	129	107	102	75	76	86	119	105	95
CKD Stage	5	1	1	1	2	2	2	1	1	1
24-h urine protein (mg/24h)	On Dialysis	260mg	400mg	280mg	140mg	220mg	150mg	680mg	120mg	60mg
24-h microalbumin urine (µg/min-mg/24h)	On Dialysis	Not performed	203mg	Not performed	21mg	Not performed	9,8mg	480mg	5,7mg	2,8mg
Angiokeratomas	+	+	+	-	-	-	-	-	-	-
Hypodrosis	+	-	-	+	+	-	+	+	+	-
Gastrointestinal Symptoms	+	+	-	+	-	-	-	-	-	+
Cornea Verticilata	+	+	+	+	+	+	+	+	+	+
Acroparesthesias	+	+	+	+	+	+	+	+	+	+
Left Ventricular Hipertrophy	+	-	-	+	+	+	-	-	-	-

Tabel 2: Kidney biopsy – glomerular, vascular, tubular and interstitial pathologic findings

	Male, 25y Nephew	Female, 49y Sister	Female, 47y Sister	Female,30y Niece	Female, 27y Niece	Female, 22y Daughter	Female, 16y Daughter
Podocyte vacuolization	+	+	+	+	+	+	+
Glomerular sclerosis	+ (1/22)	-	+ 1/40	-	-	-	-
Glomerular endothelial cells inclusions	+	-	+	-	-	-	-
Segmental foot-process effacement	+	+	+	+	+	+	+
Interstitial fibrosis	10%	5%	5%	5%	5%	-	-
Vascular inclusions	+	-	+	+	-	+	+

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