Abstract citation ID: gfae069.1420

#1575

Cardio-renal syndrome in patients with Fabry disease on enzyme replacement therapy

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Background and Aims: Fabry disease (FD) is a rare X-linked lysosomal storage disorder in which mutations of the GLA gene cause a decreased or absent activity of the alpha-galactosidase A (α-Gal A) and intracellular accumulation of globotriaosylceramide and other sphingolipids [1]. FD causes a variety of symptoms, including heart and kidneys damage - cardiorenal syndrome (CRS) type 5. In patients with FD, CRS is known to increase the risk of cardiovascular events and death [2].

The aim of our study was to assess renal function and outcomes in patients with FD and CRS receiving enzyme replacement therapy (ERT).

Method: We performed a retrospective analysis of the medical records of 10 patients (pts) from 7 unrelated families with established diagnosis of FD and cardiac and renal involvement. Pts #1 and #3 are siblings, pt # 10 is their mother; pt #9 is mother of pt #8 (Table 1). The diagnosis was confirmed by DNA diagnostics in all plus levels of α-Gal A enzymatic activity, globotriaosylsphingosine concentrations in some patients. All the patients underwent ERT. Seven out of 10 patients received blockers of the renin-angiotensin-aldosterone system, 3 - did not receive due to contraindications.

Results: All 10 patients, including 3 women, had left ventricular hypertrophy - left ventricular wall thickness (LVWT) $\geq$ 1.2 cm. (Table 1). Average LVWT was 1.850 $\pm$ 0.097 cm. Two patients had atrial fibrillation. None of the patients had proteinuria 1 g/24 h or higher. In all eGFR was below 60 ml/min/1,73 m2: 4 patients had CKD-G3a, 4 – G3b, 1 – G4 and 1 – G5. Average eGFR was 41,111 $\pm$ 8.069 ml/min/1,73 m2 excluding hemodialysis (HD) patient.

There were 4 unfavorable outcomes in our group: death occurred in 3 patients from cardiac pathology (congestive heart failure), one patient reached CKD-G5 at 25 years of age and started HD treatment. Patient on HD, brother of deceased pt #1, began receiving ERT after the start of renal replacement therapy. The death of pt #1, who had a very high Lyso-Gb3 level - 118.36 ng/ml (normal 0.05-3.0 ng/ml), appears to be related to the late diagnosis and delayed start of ERT.

Conclusion: Patients with FD and CRS are likely to have a high risk of cardiovascular complications, loss of kidney function and death, especially with a late start of enzyme replacement and cardio-renoprotective therapy. Early diagnosis of FD and timely initiation of treatment are important in preventing the serious complications and death.

Table 1: Raw data of the patients with FD.

Patient #	1	2	3	4	5	6	7	8	9	10
Sex	M	F	M	M	M	M	M	M	F	F
Age, years	51	17	31	42	34	45	48	37	67	70
LVWT, cm	1.9	1.7	1.8	1.9	1.8	1.9	2.0	1.7	1.9	1.9
Rhythm disorders	-	-	-	-	-	AFib	-	-	-	AFib
eGFR, ml/min/1,73 m^2	37	42	HD	40	46	32	28	45	55	45
α-Gal A activity	↓	Normal	↓	↓	↓	↓	↓	↓	-	Normal
Lyso-Gb3 level	↑	↑	↑	↑	↑	-	-	-	-	↑
DNA diagnostics (mutations in gene GLA)	c.614C>G (p.P205R)	c.614C>G (p.P205R)	c.614C>G (p.P205R)	c.1231G>C (p.G411R)	c.1134T>A (p.Cys378Ter)	c.847C>A (p.Glu283Lys)	c.237delA (G80Afs*41)	c.100_101delA AinsTC (p.Asn34Ser)	c.100_101delA AinsTC (p.Asn34Ser)	c.614C>G (p.P205R)
Cardio-renoprotective therapy	ARB	ACEi	-	ARB	ARB	-	-	ACEi	ACEi	ACEi
ERT, years	1.5	4	4	5	4	12	6	10	1	1
Outcome	Death	S/V	S/V (on HD)	Death	Death	S/V	S/V	S/V	S/V	S/V

*Notice: LVWT - left ventricular wall thickness; AFib - atrial fibrillation; eGFR - estimated glomerular filtration rate; HD - hemodialysis; α-Gal A - α-galactosidase A; Lyso-Gb3 - globotriaosylsphingosine; ARB - angiotensin receptor blocker; ACEi - angiotensin-converting enzyme inhibitor; ERT - enzyme replacement therapy; S/V - under supervision.

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