CLINICAL SIGNIFICANCE OF GENETIC VARIANTS IN PATIENTS WITH C3 GLOMERULOPATHIES

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OBJECTIVES

C3 glomerulopathies (C3Gs) are a recent disease classification comprising several rare types of glomerulonephritis (GN), including C3 glomerulonephritis, dense deposit disease and CFHR5 nephropathy. Isolated C3 deposition within the glomerulus is the defining histological criterion for C3Gs. Abnormal regulation of alternative pathway of complement system due to hereditary or acquired reasons leads this process. Although knowledge about C3Gs increases, genetic defects have not been fully elucidated yet. The thrombotic microangiopathies (TMAs) and C3Gs include a spectrum of rare diseases, and they share phenotypic similarities and underlying genetic commonalities. Herein, we reported genetic results associated with atypical hemolytic uremic syndrome (aHUS) and C3Gs and outcomes of 5 patients who had diagnosis of C3Gs.

METHODS

Five patients (4 male, 1 female) with kidney biopsies that fulfilled criteria for C3 glomerulopathy were evaluated. The following tests were performed in all five patients: serum C3 and C4 levels, C3 nephritic factor (C3NeF) and genetic screening for CFH, CFI, CFB, CD46, C3, C5, DGKE, CFHR1, CFHR 3, CFHR5, THBD and ADAMTS13 mutations and risk haplotypes associated with aHUS.

RESULTS

Demographic / Clinical Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Male	Male	Male	Female
Age (years)	23	26	31	49	23
Age at biopsy (years)	15	20	22	38	13
Follow-up (months)	96	78	98	131	112
Laboratory data at biopsy					
Proteinuria (Up/c) (g/day)	1	6.9	3.6	4	4
Serum creatinine (mg/dL)	0.8	0.8	3,5	3	0,5
eGFR (ml/min/1.73 m^2)					
Serum C3 levels (mg/dL)	17	14	66		34
Serum C4 levels (mg/dL)	21	23	26		20
C3NeF	Positive	Positive			Positive
Genetic abnormality	None	CFH p.Gln950His C3 p.Ala1286Thr	CFH p.Gln936Asp	CFB p.Leu9His C5 p.Gln1437Asp	CFH p.Asn1050Tyr
Outcomes	Dialysis	Hemodialysis	Hemodialysis	Hemodialysis	Remission

All patients received immunosuppressive treatment with prednisolone, mycophenolate mofetil and 2 had Eculizumab on follow ups. Complete remission was observed in 1 patient who was on prednisolone and MMF treatment. Four of 5 patients were progressed to end stage renal disease in whom 3 of them had renal transplantation and 1 was on peritoneal dialysis. Serum C3 levels were low in all patients, C3Nef was positive in 3 of 5 patients. Demographic and laboratory findings are shown on table. Genetic variants in CFH (patient 2, 3, 5), CFB (patient 4), C5 (patient 4) and C3 (patient 2) genes were demonstrated in 4 of 5 patients.

CONCLUSIONS

C3 Gs are a novel disease entity with a high risk of progression to end stage kidney disease. In majority of patients acquired or genetic defects in alternative pathway regulation can be demonstrated. Studies have provided better understanding of genetic relation among aHUS patients whereas knowledge of genetics of C3Gs is not yet fully understood. Pathogenic genetic variants associated with aHUS seem to be genetic drivers of C3Gs among our patients in whom deterioration in kidney function could not be prevented despite immunosuppressive and anti-complement treatment.

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