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Case Report

C3GN associated with deletion in CHFR1 and CHFR3 genes: a case report

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ABSTRACT

C3GN is a unique abnormality that commonly occurs due to an abnormal alternative path of the complement complex. This is distinguished by precipitation of mainly the C3 factor of complement along with minimal deposit of immunoglobulin in the mesangial, subepithelial, and subendothelial areas of glomeruli. It is seen that most of the mutations that are pathogenic happen in C3, complement factor B (CFB), complement factor H (CFH), complement factor I, along with CFHR5. Some other associations are also found that could lead to this disorder, such as autoantibodies against C3 nephrotic factor, C5 nephritic factor, anti-CFB autoantibodies, along with anti-CHF antibodies. Atypical HUS occurs due to abnormality in different components of the alternate pathway, such as complement factor F, and autoantibodies against anti-CFH caused by CFHR 1 and 3 deletions. Here we narrate a rare occurrence of C3GN related to mutation in CFHR1 and 3 in a young female and her mother who presented to us for renal transplant as prospective recipient with her mother as donor

Keywords: C3GN, aHUS, CHFR 1 gene, CHFR 3 gene, Dense deposit disease, MPGN

INTRODUCTION

Various types of renal diseases are caused due to abnormal regulation of the alternative pathway of the complement complex, such as atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G). They constitute complement-triggered glomerular diseases.[1] Abnormal regulation in the alternative pathway leads to C3 glomerulopathy which is identified by the accumulation of mainly the C3 component of complement, including or excluding immunoglobulin deposition in mesangial and subepithelial areas, along with subendothelial areas in the glomeruli.[2]

On histopathology, it is divided into two categories: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

DDD, also called membranoproliferative glomerulonephritis (MPGN) type II, is mostly distinguished by dense osmophilic intramembranous depositions in the glomeruli. As compared to this, C3GN on histopathology is distinguished by mainly C3 depositions in the subendothelial and subepithelial areas along with the mesangial area in the glomeruli.[2]

Abnormalities that lead to C3GN could be inherited/ acquired. Genetic aberrations include pathogenetic mutations in various complement-related genes like C3, CFB, CFH, complement factor I, and CFH-related protein 5. Acquired disorders occur due to the formation of various autoantibodies opposed to various complement proteins. Examples of these are C3 nephritic factor (C3NeF) that aimed at C3 convertase, C5NeF that aimed at C5 convertase, anti-CFH autoantibodies, and anti-CFB

autoantibodies.[3] These antibodies were first discovered as an important cause leading to HUS in 2005.[4,5]

Here we narrate a case of C3GN due to CFHR1/ CFHR3 deletion in both daughter and mother along with a literature search.

CASE REPORT

A female patient of age twenty-two years presented to our OPD as a prospective renal transplant recipient. Her history dates ten years back, when she developed generalized weakness, which on evaluation, was found to be anemia, and she was advised to take supplements. She symptomatically improved. After one year she developed swelling in bilateral lower limbs and periorbital puffiness. Again, hemoglobin was checked, and iron and folic acid supplements were advised. No renal function test was done. After one year her edematous illness worsened, and her appetite decreased.

On investigations she was found to have anemia and renal dysfunction. Autoimmune profile done at that time was normal. Examination of urine was done, which indicative of microscopic hematuria and proteinuria (Table 1).

Renal biopsy was done which was indicative of MPGN pattern and predominantly C3 deposits were found on immunofluorescence. The patient was explained about the high chronicity in biopsy and need for renal replacement therapy in future. She was given immunosuppression in the form of steroids along with mycophenolate mofetil. Immunosuppression was stopped after 3 months.

There was progressive derangement in her renal functions, and she was declared dialysis dependent and was started on maintenance hemodialysis after four years. Her purpose in visiting us was renal transplant along with her mother as a prospective donor. During evaluation for pretransplant workup, it was found that her C3 levels were low. The possibility of C3GN was kept.

For her and her mother, whole exome sequencing and multiplex ligation-dependent probe amplification tests were done. On which it was found that heterozygous deletion in CFHR3 and CFHR1 was present in the patient and homozygous deletion in CFHR3 and CFHR1 was present in her mother (Figure 1 and 2).

Table 1: Investigations of patient.

Parameters	Values
Haemoglobin	6.5 gm/dl
TLC	4.9×10^3/ul
Platelet count	157×10^3/ul
Urea/creatinine	188/11.05 mg/dl
Albumin	2.2 gm/dl
Cholesterol/triglyceride	170/290 mg/dl
24-hour urine protein	1460 mg/day
C3/C4	116/39.6

Sl. No.	Deletions /Duplications	No. of exons deleted/duplicated ♦	MLPA probe ratio (Dosage quotient) #	Disease (OMIM)	Inheritance
1.	Heterozygous deletion	*CFHR3* (Upstream region, exons 1, 2, 3, 4, 6 and intron 4), *CFHR1* (introns 1, 3 exons 2, 4, 5, 6)	0.44 – 0.61	Hemolytic uremic syndrome, atypical	Autosomal dominant, Autosomal recessive

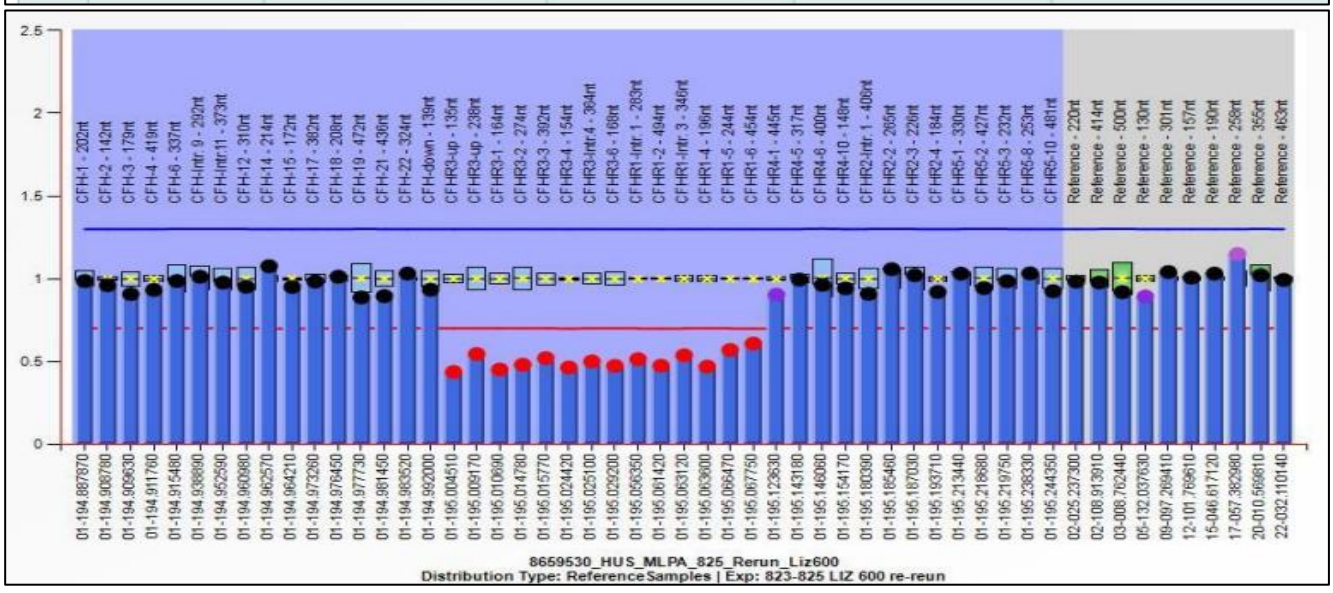

Figure 1: Whole exome sequencing and multiplex ligation-dependent probe amplification tests of patient.

Sl. No.	Deletions /Duplications	No. of exons deleted/duplicated †	MLPA probe ratio (Dosage quotient) #	Disease (OMIM)	Inheritance
1.	Homozygous deletion	*CFHR3* (Upstream region, exons 1, 2, 3, 4, 6 and intron 4), *CFHR1* (introns 1, 3 exons 2, 4, 5, 6)	0.00– 0.24	Hemolytic uremic syndrome, atypical	Autosomal dominant, Autosomal recessive

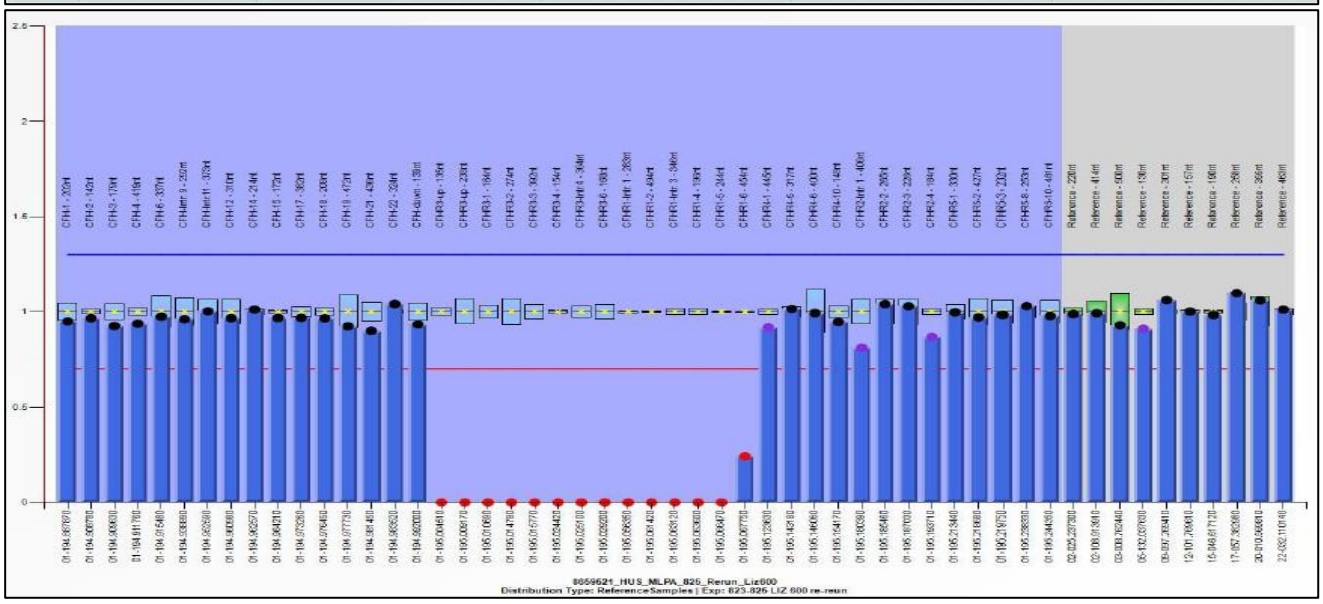

Figure 2: Whole exome sequencing and multiplex ligation-dependent probe amplification tests of mother.

DISCUSSION

MPGN is a heterogenous category of diseases occurs in glomeruli due to abnormal regulation of the complement system causing precipitation of C3 and breakdown products of complement. C3G is mainly present at a young age although it can present at any age. CFH is the main regulator of the alternative pathway in the complement system in both fluid phase as well as cell surfaces.[6]

The gene family of CHF comprises the CFH, CFHR1, CFHR2, CFHR3, CFHR4, and CFHR5 genes on chromosome 1q31.3.[7]

In this case report, we outline C3GN associated with CFHR1 and CFHR3 deletion in a young female presented with ESRD and her mother during workup for renal transplant. The possibility of C3GN was kept due to low C3 levels. Genetic workup was sent as there is a high probability of recurrence in C3GN. It was found that heterozygous deletion in CFHR3 and CFHR1 was present in our patient and homozygous deletion in CFHR3 and CFHR1 was present in her mother.

In a previous study, it was found that loss of both CFHR3 and CFHR1 was related to decreased chances of age-related macular degeneration and IgA nephropathy but increased possibility of aHUS.[8,9] Deletion of CFHR3 and CFHR1 leading to break in cell surface protection, which can lead to aHUS.[10] More often, deletions related to aHUS are CFHR3 and CFHR1 deletions.

High chances of recurrence are seen in patients with mutations in the CFH gene or in carriers of the hybrid gene. So, we explained to our patient the poor prognosis and high recurrence risk with the donor as her mother.

CONCLUSION

Rare case of C3GN-associated with CFHR1/CFHR3 gene deletions in an adult Indian female and her mother. So, we emphasize the significance of genetic testing and complement factor assay in prospective renal transplant recipients with low C3 levels.

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