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ORIGINAL ARTICLE

# Complement gene mutations in children with C3 glomerulopathy: do they affect the response to mycophenolate mofetil?

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## Abstract

**Background** C3 glomerulopathy (C3G) is a complement-mediated disease. Although genetic studies are not required for diagnosis, they are valuable for treatment planning and prognosis prediction. The aim of this study is to investigate the clinical phenotypes, kidney survival, and response to mycophenolate mofetil (MMF) treatment in pediatric C3G patients with and without mutations in complement-related genes.

**Methods** Sixty pediatric C3G patients were included, divided into two groups based on complement-related gene mutations. Demographic and clinical-pathological findings, treatment modalities, and outcome data were compared, and Kaplan–Meier analysis was performed for kidney survival.

**Results** Out of the 60 patients, 17 had mutations. The most common mutation was in the *CFH* gene (47%). The mean age at diagnosis was higher in the group with mutation (12.9 ± 3.6 vs. 11.2 ± 4.1 years, $p = 0.039$). While the patients without mutation most frequently presented with nephritic syndrome (44.2%), the mutation group was most likely to have asymptomatic urinary abnormalities (47.1%, $p = 0.043$). Serum parameters and histopathological characteristics were similar, but hypoalbuminemia was more common in patients without mutation. During 45-month follow-up,10 patients progressed to chronic kidney disease stage 5 (CKD5), with 4 having genetic mutation. The time to develop CKD5 was longer in the mutation group but not significant. MMF treatment had no effect on progression in either group.

**Conclusions** This study is the largest pediatric C3G study examining the relationship between genotype and phenotype. We showed that the mutation group often presented with asymptomatic urinary abnormalities, was diagnosed relatively late but was not different from the without mutation group in terms of MMF treatment response and kidney survival.

**Keywords** C3 glomerulopathy · C3 glomerulonephritis · Children · Complement system · Genetic · Rare disease

## Introduction

C3 glomerulopathy (C3G) is a rare glomerular disease, which develops due to dysregulation of the alternative complement pathway and affects both adults and children [1–3]. The membranoproliferative pattern of injury on light microscopy (LM) and the predominance of glomerular C3 staining on immunofluorescence (IF) microscopy with minimal or no immunoglobulin deposition are striking histopathological features [4]. The density of C3 deposition in electron microscopy (EM) distinguishes between C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), two distinct entities.

While C3 deposits in DDD are more strongly present in the mesangium and glomerular basement membrane and form a distinctive ribbon-shaped band, C3 deposits in C3GN are dispersed throughout the mesangium and capillary walls [2, 4].

Clinical presentation may vary from microscopic hematuria to rapidly progressive glomerulonephritis. However, patients often present with proteinuria without impaired kidney function [1, 5]. Although C3G has a known poor

Extended author information available on the last page of the article

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prognosis, spontaneous remission is rarely possible [1]. The median time from diagnosis to kidney failure is 10–15 years [2, 6, 7]. Progression to stage 5 chronic kidney disease (CKD5) within 10 years of diagnosis has been reported to be 50%, regardless of histologic type [2, 5, 8]. However, these are mainly data from adult studies and have reported a negative correlation between age at diagnosis and long-term kidney survival [2, 5, 6, 8]. In pediatric studies, kidney survival has been found to be better than in adults [7, 9, 10].

As previously shown, lower serum albumin and estimated glomerular filtration rate (eGFR) at diagnosis [10], nephritic syndrome at onset [11], crescentic GN [2, 11], severity of glomerulosclerosis [11] and degree of tubular atrophy and interstitial fibrosis [12], DDD subtype [2] at the time of biopsy, and absence of mutations or C3 nephritic factors (C3NeF) [11] were found to be independent predictors for poor kidney outcome.

Underlying causes of the disease can either be inherited causes, such as pathogenic mutations in the complement genes, or acquired factors, such as antibodies against the regulators of the complement system and nephritic factors. Patients may have the mutation, antibodies, or both [13].

There is currently no evidenced-based treatment modality for C3G [14]. Treatment options include supportive therapy, immunosuppressives, and anticomplement treatments. The combination of corticosteroid and mycophenolate mofetil (MMF) is the most preferred treatment regimen, and the efficacy of this regimen has been demonstrated in several studies [15, 16]. Although there are limited data, some studies have suggested that individuals with pathogenic variants in complement genes have a less favorable response to treatment [12, 17].

There is limited data about genotype and phenotype correlations in C3G [1, 18]. For choosing the best-fitting treatment and a better prognosis prediction, genetic research on C3G is required. The aim of this study is to investigate the clinical differences and response to MMF treatment of pediatric C3G patients with and without mutations in complement-related genes.

## Methods

### Design of study

The Turkish Children's C3 Glomerulopathy Study Group, a working group of the Turkish Society of Pediatric Nephrology founded in 2017, conducted this research. This study protocol was approved by the local institutional Ethics Committee (2017/209) to comply with Helsinki clinical research standards. A registration form was emailed to clinical centers to enter data on patients before the age of 18 who were diagnosed with C3G and had a genetic screening for the complement genetic mutations and were followed for at least 6 months between 2006 and 2022. Eighteen pediatric nephrology centers from 11 provinces in Turkey were included in the study.

### Data

Sixty patients younger than 18 years of age, whose diagnosis of C3G was defined based on the 2013 C3G consensus guidelines, were included in the study. According to this guideline, the injury pattern of membranoproliferative glomerulonephritis (MPGN) in LM and predominant C3 staining with or without insufficient Ig deposition in IF were determined as C3G [4]. The data of 27 patients who took part in a prior study conducted by the same study group were also included in this investigation [10] (see Supplementary Materials). Patient demographic data, laboratory parameters (blood urea nitrogen, serum creatinine, albumin, C3 and C4 levels, and urine protein/creatinine ratio) and clinical characteristics at admission (nephrotic syndrome, nephritic syndrome, or asymptomatic urinary abnormality), treatments used, histopathological findings of kidney biopsy, and C3NeF positivity were recorded. All patients underwent genetic testing for mutations in the activation proteins (CFB, C3, and C5) or regulatory proteins (CFH, CFI, CD46, CFHR3, CFHR5, and CFHR1) that control the alternative complement pathway. Based on the mutant allele frequency (MAF) bioinformatics analysis and functional evidence and using the criteria of the American College of Medical Genetics and Genomics, variations were classified as variant(s) of unknown significance (VUS), likely pathogenic, and pathogenic [19]. Patients were classified according to whether or not they had any mutations.

According to the medical treatments given, the patients were divided into two groups: those who received MMF at any time during their follow-up and those who did not. The endpoint for kidney survival was decided to be CKD5, which was defined as having an eGFR of less than 15 mL/min/1.73 $m^2$ or having chronic dialysis or kidney transplantation.

MMF treatment was given at a dose of 600–1200 mg/$m^2$/day. The MMF dose was adjusted by the clinician according to the patient's condition; however, MMF level was not measured.

### Definitions

Blood in the urine, visible to the naked eye, was regarded as gross hematuria, while microscopic hematuria was defined by the presence of > 5 RBC per high power field. Non-nephrotic range proteinuria (4–40 mg/$m^2$/h or PCR 0.2–2 mg/mg) was used to describe abnormal proteinuria. Nephrotic syndrome was described as edema, a serum albumin level below 3 g/dL, and nephrotic range proteinuria [> 40 mg/$m^2$/h or protein to creatinine ratio (PCR) > 2 mg/mg]. Nephritic syndrome was defined as macroscopic hematuria, edema, and hypertension. The occurrence of chronic microscopic hematuria and/or non-nephrotic proteinuria were considered to be asymptomatic urine abnormalities. Patients with asymptomatic urinary abnormalities were detected during an infection or routine

control. In the follow-up of these patients, C3G was diagnosed when urinary findings persisted and progressed. Hypertension was defined as blood pressure > 95th percentile for sex, age, and height. Hypoalbuminemia was defined as a serum albumin level below 3 g/dL. Modified Rabasco criteria were used to evaluate treatment responses [15]. Partial remission (PR) was defined as maintained or increased eGFR with 50% reduction in proteinuria at last follow-up. Complete remission (CR) was defined as normal serum albumin (> 3 g/dL) and eGFR > 90 mL/min/1.73 $m^2$ without proteinuria (4 mg/$m^2$/h or PCR 0.2 mg/mg). Children classified as "responders" had either CR or PR. Children who did not have either a CR or PR were referred to as "non-responders." CKD5 was defined as requiring chronic dialysis or a kidney transplant or having an eGFR of less than 15 mL/min/1.73 $m^2$.

### Statistical analysis

The SPSS Statistics version 22.0 program (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses. The normality of continuous data was examined using the Shapiro–Wilk test. Mean ± standard deviation (SD) was used to express normally distributed data, and median (interquartile range (IQR)) was used to express non-normally distributed data. Categorical variables were analyzed using the Fisher exact t-test and the Pearson chi-square test. The Student *t*-test or the Mann–Whitney *U* test was used to compare the means of continuous variables between two groups.

Age, gender, follow-up period, laboratory parameters at admission, clinical presentation, development of CKD5 during follow-up, treatments given, cumulative doses of prednisolone, and histopathological features in biopsy were compared in patients with and without genetic mutations.

Kaplan–Meier analysis was performed to compare kidney survival between the groups with and without mutation. Additionally, Kaplan Meier analysis was used to evaluate kidney survival between MMF users and non-users. Each patient's kidney survival time was estimated from the time of diagnosis until the time of their last evaluation or the time they started receiving kidney replacement therapy, or the time they reached an eGFR of less than 15 mL/min/1.73 $m^2$. A $p$-value of $< 0.05$ was considered statistically significant.

## Results

Sixty patients from 18 centers were included in the study. A total of 53.3% ($n = 32$) of patients were female. The mean age on admission and at the time of diagnosis was 10.6 ± 4.3 and 11.2 ± 4.1 years, respectively. The median follow-up time was 45 months (Q1, 25.5; Q3, 68). Parental consanguinity rate was 33.3%. On admission, 15 patients (25%) had asymptomatic urine abnormalities, 22 patients (36.7%) had nephrotic syndrome, and 23 patients (38.3%) had nephritic syndrome (Table 1).

On admission, the mean eGFR was 109.4 ± 49.5 mL/min/1.73 $m^2$, and 76% of the patients had low C3 levels. C3NeF analysis was performed in only 22 patients, and 11 of them had positivity. Membranoproliferative glomerulonephritis was the most common pattern of kidney injury on biopsy with a rate of 67%. Dense deposit disease was found in 11 patients (18.3%) on EM (Table 1).

The treatment modalities were classified as prednisolone + MMF, MMF + other immunosuppressive (IS) medications (cyclosporine, cyclophosphamide, azathioprine, rituximab, and eculizumab), and MMF-free immunosuppression (IS). 16 patients (26.7%) received MMF-free IS therapy, 12 patients (20%) were treated with prednisolone plus MMF only, and 32 patients (53.3%) received MMF plus at least one of the other IS medications. When patients with and without MMF treatment were compared with respect to other treatments (ACEI, eculizumab, cyclosporine, cyclophosphamide, azathioprine, and rituximab), there was no significant difference between the two groups in terms of treatment distribution and duration (see Supplementary Table 1).

### Comparison of groups with and without mutations

Mutations in complement system regulating genes were detected in 17 of 60 patients (28%). The mutations were mostly in *CFH* (47%) and *CFB* (23.5%) genes (Tables 2 and 3).

There was no difference in age, gender, or consanguinity between patients with and without the mutation, but patients with the mutation were older at diagnosis ($p = 0.039$) and had longer follow-ups ($p = 0.038$) (Table 2). The initial clinical presentation was quite different between the two groups ($p = 0.043$). The most common clinical presentation was nephritic syndrome (44.2%) in patients having no mutation, but asymptomatic urinary abnormalities (47.1%) in patients with mutation.

There were no significant differences in BUN, serum creatinine, eGFR, C3, or C4 levels on admission, but hypoalbuminemia was more frequent in patients without mutation ($p = 0.008$). The number of patients with C3NeF positivity was higher in patients without mutation than in patients with mutation (56% vs. 33%), but the difference did not reach statistical significance (Table 2). DDD was detected in 23.5% and 16.3% of the groups with or without mutations, respectively, but the difference was not significant. MMF exposure at any time during their follow-up was similar in patients with or without

**Table 1** Clinical and histological features of the study group

| | | |
|---|---|---|
| Age at admission, years (mean ± SD) | | 10.6 ± 4.3 |
| Age at diagnosis, years (mean ± SD) | | 11.2 ± 4.1 |
| Follow-up time, months (median (Q1–Q3)) | | 45 (25.5–68) |
| Girl, *n* (%) | | 32 (53.3%) |
| Consanguineous marriage, *n* (%) | | 20 (33.3%) |
| Clinical presentation, *n* (%) | Nephrotic syndrome | 22 (36.7%) |
| | Nephritic syndrome | 23 (38.3%) |
| | Asymptomatic urinary abnormality | 15 (25.0%) |
| Laboratory parameters on admisssion | BUN, mg/dL (median (Q1–Q3)) | 16 (12–29.5) |
| | Cr, mg/dL (median (Q1–Q3)) | 0.6 (0.45–0.85) |
| | First eGFR (mean ± SD) | 109.4 ± 49.5 |
| | First eGFR < 60, *n* (%) | 9 (15%) |
| | Last eGFR (median (Q1–Q3)) | 112.2 (73.4–140.7) |
| | Last eGFR < 60, *n* (%) | 12 (20%) |
| | Albumin, gr/dL (mean ± SD) | 2.8 ± 1.0 |
| | Albumin < 3 gr/dL, *n* (%) | 35 (58.3%) |
| | C3, mg/dL (median (Q1–Q3)) | 30 (17.4–69) |
| | C3 < 70 mg/dL, *n* (%) | 46 (76.7%) |
| | C4, mg/dL (median (Q1–Q3)) | 19.5 (13.6–23.6) |
| | C4 < 15 mg/dL, *n* (%) | 17 (28.3%) |
| | Nephrotic range proteinuria, *n* (%) | 48 (81.7%) |
| | C3 nephritic factor positivity, *n* (%) | 11 (50%) |
| Genetic mutation, *n* (%) | *CFH* | 8 (47%) |
| | *CFI* | 2 (11.7%) |
| | *CFB* | 4 (23.5%) |
| | *C3* | 1 (5.8%) |
| | *CFHR3* | 2 (11.7%) |
| | *THBD* | 1 (5.8%) |
| | *CD46* | 1 (5.8%) |
| | Multiple | 3 (17.6%) |
| Distrubution of genetic mutation, *n* (%) | Pathogenic variants | 6 (10%) |
| | Variants of unknown significance | 11 (18.3%) |
| | None | 43 (71.7%) |
| Histopathological features | | |
| Light microscopy, *n* (%) | Membranoproliferative GN | 40 (66.6%) |
| | Mesangial proliferative GN | 25 (41.7%) |
| | Crescentic GN | 15 (25%) |
| | Arteriolar sclerosis | 10 (16.7%) |
| | Interstitial fibrosis | 15 (25%) |
| | Global sclerosis | 23 (38.3%) |
| Immunofluorescence, *n* (%) | C3 | 60 (100%) |
| | C4 | 4 (6.7%) |
| | C1q | 12 (20%) |
| | IgA | 2 (3.3%) |
| | IgG | 12 (20%) |
| | IgM | 22 (36.7%) |
| Electron microscopy, *n* (%) | C3 | 49 (81.7%) |
| | DDD | 11 (18.3%) |
| Treatments, *n* (%) | Only MMF + prednisolone | 12 (20%) |
| | MMF + others | 32 (53.3%) |
| | Non-MMF | 16 (26.7%) |

**Table 1** (continued)

| | | |
|---|---|---|
| Outcomes, *n* (%) | GFR < 15 | 3 (5%) |
| | Dialysis | 5 (8.3%) |
| | KTx | 2 (3.3%) |
| | Remission | 43 (71.7%) |
| | Active disease | 7 (11.7%) |
| | Total | 60 (100%) |

mutations (75.3% and 70.6%, respectively). There was also no statistically significant difference between the two groups in terms of cumulative prednisolone doses. Regarding other therapies, the number of patients who received eculizumab was higher in the mutation group, but there was no difference between the groups in terms of use of other immunosuppressive treatments (Table 2).

## Outcomes

There was no difference between the two groups in terms of study outcomes (CKD5) and the requirement for dialysis on admission (Table 2).

Kidney outcomes were evaluated based on the clinical and laboratory findings at last follow-up. Complete remission or PR was obtained in 43 patients (71.7%). Seven patients still had active disease. 10 patients (16.6%) reached CKD5 with 3 of them in pre-dialysis, 5 of them on dialysis, and 2 of them having kidney transplants. There were no deaths in the study group. The time to remission was shorter in patients without mutation ($9.3 \pm 7.4$ months vs. $13.5 \pm 11.1$ months), but the difference was not statistically significant ($p = 0.09$). Kidney outcomes were similar between the two groups ($p = 0.451$).

In Kaplan–Meier analysis, time to CKD5 was longer in patients with mutation compared with those without mutation ($139.1 \pm 30.5$ months vs. $110.4 \pm 9.7$ months). The difference was not statistically significant. The response to MMF treatment was similar between groups, and in 17 patients having the mutation, this treatment did not affect kidney survival (Table 4).

## Discussion

This study is the first multicenter C3G series of pediatric patients to show data on the effects of genotype and MMF treatment on clinical outcomes. Patients' initial clinical phenotype may vary depending on whether they have mutations or not and may not influence kidney outcomes, unlike previous adult studies [11, 20]. Additionally, MMF treatment was unable to show any kidney survival benefit in both patients with and without complement gene mutations.

Currently, in children and adults, the diagnosis of C3G is based on biopsy [4]. Although genetic testing is not necessary to make a diagnosis, it has been shown that it can provide a perspective in evaluating the treatment response and in predicting the prognosis of the disease [18, 21]. Therefore, efforts to confirm the disease with genetic confirmation are increasing with expert opinions [22]. In this study, we examined the relationship between genotype and phenotype in children with C3G and the effect of MMF treatment on the clinical outcomes of patients with C3G.

According to extensive genetic studies, 25–41% of patients with C3G have rare or unique variants in complement-related genes [6, 11, 23]. Contrary to the high genetic mutation expectation in the pediatric population in general, this rate was found as 28.3%, which is quite similar to adult cohorts. Although there are different rates in studies, the distribution of variants in complement genes is predominantly seen in complement regulatory genes (*CFH, CFI, CD46*) and activation protein genes (*C3, CFB*) [1, 4]. In the study by Zhao et al. [20] variants were detected in *CFH*, *CFI*, *CD46*, and *C3* genes and found to be similar to the studies by Servais et al. and Bu et al. [6, 23]. These studies were conducted in Caucasians. Iatropoulos et al. observed that the highest frequency of genetic abnormalities was found in *C3* (50%), followed by *CFH* (21%) and *CFB* (3%) [11]. In our study, mutations in *CFH* (47%) and *CFB* (23.5%) genes were the most frequently detected mutations. C3 mutation was detected in only 1 patient (5.8%) (Table 1). These genetic differences may be due to genetic heterogeneity between populations.

Known pathogenic variants were detected in only 4 of 17 patients with mutations in our study. Of the remaining, 2 were likely pathogenic variants and the others were variants of unknown significance. In addition, 3 patients were found to carry multiple variants in complement-related genes. Carrying multiple variants in complement-related genes in C3G is not unexpected. It is thought that this complex genetic

**Table 2** Comparison of clinical and laboratory parameters according to mutation status

| | Genetic analysis | | |
|---|---|---|---|
| | Mutation Ø ($n=43$) | Mutation + ($n=17$) | $p$ |
| Girl, $n$ (%)* | 23 (53.5%) | 9 (52.9%) | 1.000 |
| Age at diagnosis, year (mean ± SD)** | 10.5 ± 4.1 | 12.9 ± 3.6 | **0.039** |
| Follow-up time, months (median (Q1–Q3))*** | 35 (23–58) | 59 (43–86) | **0.034** |
| Consanguineous marriage, $n$ (%) | 14 (33.3%) | 6 (35.3%) | 1.000 |
| Laboratory parameters | | | |
| BUN, mg/dL (median (Q1–Q3))*** | 16.5 (12.8–32) | 12.8 (9.9–20) | 0.055 |
| Creatinine, mg/dL (median (Q1–Q3))*** | 0.6 (0.48–0.88) | 0.58 (0.41–0.79) | 0.506 |
| First eGFR (mean ± SD) | 103.4 ± 50.9 ($n=42$) | 124.2 ± 43.3 ($n=17$) | 0.145 |
| First eGFR < 60, $n$ (%) | 8 (19) | 1 (5.9) | 0.382 |
| Last eGFR (median (Q1–Q3)) | 116.6 ± 65.7 ($n=40$) | 92.5 ± 45.6 ($n=16$) | 0.187 |
| Last eGFR < 60, $n$ (%) | 8 (19) | 4 (15) | 0.720 |
| Albumin, gr/dL (mean ± SD) | 2.57 ± 0.95 ($n=43$) | 3.39 ± 0.95 ($n=30$) | **0.004** |
| Albumin < 3 gr/dL, $n$ (%) | 30 (69.8) | 5 (29.4) | **0.008** |
| C3, mg/dL (median (Q1–Q3)) | 30 (18–69) | 30 (16–67.4) | 0.935 |
| C3 < 70 mg/dL, $n$ (%) | 33 (76.7%) | 13 (76.5%) | 1.000 |
| C4, mg/dL (median (Q1–Q3)) | 19 (14–23) | 21.3 (13–32) | 0.282 |
| C4 < 15 mg/dL, $n$ (%) | 12 (27.9%) | 5 (29.4%) | 1.000 |
| Nephrotic range proteinuria, $n$ (%)* | 36 (83.7%) | 13 (76.5%) | 0.772 |
| Nephritic factor positivity, $n$ (%)* | 9 (56%) | 2 (33.3%) | 0.634 |
| Clinical presentation, $n$ (%)* | | | |
| Nephrotic syndrome | 17 (39.5%) | 5 (29.4%) | **0.043** |
| Nephritic syndrome | 19 (44.2%) | 4 (23.5%) | |
| Asymptomatic urinary abnormality | 7 (16.3%) | 8 (47.1%) | |
| Dialysis requirement at the time of admission, $n$ (%)* | 4 (9.3%) | 2 (11.8%) | 0.551 |
| CKD5 development at follow-up, $n$ (%)* | 6 (14.0%) | 4 (23.5%) | 0.448 |
| First remission time at follow-up (median (Q1–Q3)*** | 5 (3–13.5) | 8 (3–16) | 0.908 |
| Histopathological features | | | |
| Light microscopy, $n$ (%)* | | | |
| Membranoproliferative GN | 28 (65.1%) | 12 (70.6%) | 0.769 |
| Mesangial proliferative GN | 17 (39.5%) | 8 (47.1%) | 0.809 |
| Crescentic GN | 12 (28.6%) | 3 (17.6%) | 0.516 |
| Arteriolar sclerosis | 7 (16.3%) | 3 (17.6%) | 0.260 |
| Interstitial fibrosis | 11 (25.6%) | 4 (23.5%) | 1.000 |
| Global sclerosis | 15 (34.9%) | 8 (47.1%) | 0.562 |
| Immunofluorescence, $n$ (%)* | | | |
| C3 | 43 (100) | 17 (100) | |
| C4 | 3 (7) | 1 (5.9) | 0.683 |
| C1q | 10 (23.3) | 2 (11.6) | 0.267 |
| IgA | 2 (4.7) | 0 (0) | 0.510 |
| IgG | 11 (25.6) | 1 (5.9) | 0.081 |
| IgM | 14 (32.6) | 8 (47.1) | 0.224 |
| Electron microscopy, $n$ (%)* | | | |
| C3 | 36 (83.7%) | 13 (76.5%) | 0.712 |
| DDD | 7 (16.3%) | 4 (23.5%) | |
| Treatments, $n$ (%)* | | | |
| Only MMF + prednisolone | 11 (26.5%) | 1 (5.9%) | 0.222 |
| MMF + others | 21 (48.8%) | 11 (64.7%) | |
| Non MMF | 11 (26.5%) | 5 (29.4%) | |

**Table 2** (continued)

| | Genetic analysis | | |
|---|---|---|---|
| | Mutation Ø ($n=43$) | Mutation + ($n=17$) | $p$ |
| Prednisolone cumulative dose, mg (median (Q1–Q3))*** | 5850 (1500–61650) | 6410 (2160–32375) | 0.519 |
| MMF initial dose, mg/m$^2$/d (median (Q1–Q3))*** | 862 (700–1200) | 1000 (624–1167) | 0.730 |
| Duration of MMF use, months (median (Q1-Q3))*** | 24 (8–33.5) | 14 (7–31.5) | 0.490 |
| Outcomes, *n* (%) | | | |
| GFR < 15 | 2 (4.7%) | 1 (5.9%) | 0.451 |
| Dialysis | 3 (7%) | 2 (11.8%) | |
| KTx | 1 (2.3%) | 1 (5.9%) | |
| Remission | 30 (69.8%) | 13 (76.5%) | |
| Active disease | 7 (16.3%) | | |
| Remission time, months (mean ± SD)** | 9.3 ± 7.4 | 13.5 ± 11.1 | 0.09 |

*Chi-square test

**Independent sample *t*-test

***Mann–Whitney *U* test

*p* values below 0.05 were considered statistically significant and shown in bold in the table

**Table 3** Genetic mutations in study group

| No | Gender/age | Gene | Variants | Mutation type | Inheritance | MAF | PP[a] | Interpretation[b] |
|---|---|---|---|---|---|---|---|---|
| 1. | M/16 | CFH | NM_000186.4: c.1696G > A, p.Glu566Lys | Heterozygous | AD/AR | No data | 5/11 | Pathogenic |
| 2. | F/18 | CFI | NM_000204.5: c.1216C > T, p.Arg406Cys | Heterozygous | AD | 1/37889 | 3/11 | VUS |
| | | CD46 | NM_172351.3: c.565 T > G, p.Try189Asp | Heterozygous | AD/AR | 1/22678 | 8/11 | LP |
| | | | NM_172359.3: c.553G > A, p.As185Asn | Heterozygous | AD/AR | 1/28428 | 3/11 | VUS |
| 3. | M/14 | CFB | NM_001710.6: c.1697A > C, p.Glu566Ala | Heterozygous | AD | No data | No data | VUS |
| | | | NM_001710.6: c.26 T > A, p.Ley9His | Heterozygous | AD | No data | No data | VUS |
| 4. | M/11 | CFH | NM_000186.4: c.380G > T, p.Arg127Leu | Homozygous | AD/AR | No data | 9/11 | Pathogenic |
| 5. | F/11 | CFH | NM_000186.4: c.1744C > T, p.R582C | Heterozygous | AD/AR | 1 in56507[1] | 3/11 | VUS |
| | | THBD | NM_000361.3: c.811G > , p.A271T | Heterozygous | AD | No data | 2/11 | VUS |
| 6. | M/9 | CFH | NM_000186.4: c.2608 T > C, p.Cys870Arg | Homozygous | AD/AR | No data | 11/13 | VUS |
| 7. | F/15 | CFB | NM_001710.6: c.94C > T, p.Arg32Trp | Heterozygous | AD | No data | No data | VUS |
| 8. | F/18 | CFH | NM_000186.4: c.2608 T > C, p.Cys870Arg | Homozygous | AD/AR | No data | 11/13 | VUS |
| 9. | F/13 | CFI | NM_001375284.1: c.782 A > G, p.Glu261Asp | Heterozygous | AD | No data | 5/13 | VUS |
| 10. | M/10 | CFB | NM_001710.6: c.26 T > A, p.Leu9His | Heterozygous | AD | No data | No data | VUS |
| 11. | M/12 | CFHR3 | NM_021023.6: c914G > A, p.Gly305Glu | Homozygous | AD/AR | 1/15549 | 6/11 | VUS |
| 12. | F/10 | C3 | NM_000064.4: c.4172 + 1 G > C, splice site mutation | Heterozygous | AD | No data | 4/4 | Pathogenic |
| 13. | M/14 | CFH | NM_000186.4: c.12204C > G, p.His402Asp | Homozygous | AD/AR | No data | 2/13 | VUS |
| 14. | F/4 | CFH | NM_000186.4: c.965_1 G > A, splice site mutation | Homozygous | AD/AR | No data | 4/4 | Pathogenic |
| 15. | F/14 | CFH | NM_000186.4: c.1748A > G, p.Lys583Arg | Heterozygous | AD/AR | No data | 1/13 | VUS |
| 16. | F/14 | CFB | NM_001710.6: c.2182 C > T, p.Gln728Ter | Heterozygous | AD | No data | 3/8 | LP |
| 17. | M/17 | CFHR3 | NM_021023.6: c.914G > A, p.Gly305Glu | Homozygous | AD/AR | 1/15549 | 6/11 | VUS |

*pp*: pathogenicity prediction; *VUS*: variant of unknown significance; *MAF*: minor allele frequency;[a] Pathogenicity prediction score using a maximum of 9 computational methods- DANN, FATHMM-MKL, M-CAP, Mutation Taster, SIFT, EIGEN, MVP, PrimateAI and REVEL.[b] Variants are interpreted as VUS , likely pathogenic, and pathogenic based on the criteria developed by the American College of Medical Genetics and Genomics

heterogeneity can partly explain why C3G penetration varies within family members [24]. The inheritance pattern in C3G can be either autosomal dominant or recessive. In our study, pathogenic mutations were detected in both heterozygous and homozygous conditions. Also, the rate of parental consanguinity was similar in the groups with and without mutations (33.3% and 35.3%, respectively).

In line with our previous studies [10, 25], a heterogeneous clinical presentation and outcome of C3G were documented. In a different case series, nephrotic syndrome was

**Table 4** Overall kidney survival according to Kaplan–Meier analysis

| Group | Time to CKD 5 (months) | 95% confidence interval | *p* |
|---|---|---|---|
| Mutation status | | | |
| Mutation + | 139.1 ± 30.5 | 79.2–199.1 | 0.980 |
| Mutation − | 110.4 ± 9.7 | 91.4–129.4 | |
| MMF treatment | | | |
| Yes | 130.9 ± 19.7 | 92.3–169.5 | 0.282 |
| No | 111.6 ± 5.9 | 99.9–123.4 | |
| MMF treatment in mutation + group | | | |
| Yes | 133.5 ± 44.9 | 45.4–221.7 | 0.572 |
| No | 99.5 ± 1.76 | 96.0–102.9 | |

the most common initial presentation, while minor urinary abnormality was reported the least [1, 13, 24, 26]. As previously shown [27], the present study revealed that nephritic syndrome in patients without mutation and asymptomatic urinary abnormalities in patients with the mutation were the leading presentations.

In this study, the albumin values of the patients without mutation were found to be statistically significantly lower than those with mutation. These results were consistent with the adult study by Zhao et al., in which they involved 43 patients with C3G and 24 patients with primary immune complex (IC)-mediated MPGN and evaluated the clinical presentation of genetically diagnosed and undiagnosed patients [20]. They found that both groups of patients had similar levels of C3, proteinuria, and nephrotic syndrome.

Membranoproliferative pattern of injury was the most common finding at biopsy (66%). This is almost like that of other groups and our previous study [3, 5, 10, 12, 17]. Diffuse proliferative GN, mesangial proliferative GN (MesPGN), and crescentic GN are other types of damage in this disease [4, 13, 28]. In our patients, MesPGN and crescentic GN were observed in 39.5% and 28.6%, respectively. In line with Zhao et al.'s study [20], the rate of crescentic GN was higher in the group with genetically diagnosed C3G; however, it did not reach statistical significance.

Currently, treatment approaches for pediatric C3G patients are based on experience and some retrospective cohort studies [22]. According to the consensus reports published by KDIGO in 2017 and 2021, a treatment plan was proposed according to the severity of the disease. In this algorithm, prednisolone and MMF took the leading roles [18, 21]. In the present study, we compared three treatment options. Prednisolone and MMF in combination were given in 26.5% of patients without mutation and 5.9% of children with mutation. There was no difference between the groups with and without mutation in terms of the treatment modalities and cumulative dosages of prednisolone.

Data on long-term outcomes with the new C3G classification are limited and vary between studies. The median time from diagnosis to kidney failure is about 10–15 years [2, 6, 7]. Progression to CKD5 within 10 years of diagnosis is reported to be 50%, regardless of histologic type [2, 5, 8]. However, these are mostly data from adult studies and have reported a negative correlation between age at diagnosis and long-term kidney survival [2, 5, 6, 8].

In pediatric studies, kidney survival has been found to be better than in adults [7, 9]. In a study by Wong et al. including 80 pediatric C3G patients, development of CKD was reported to be 14% during a median 5.18 year follow-up [7]. In our current study, the rate of development of CKD5 was 16.6% during a mean follow-up period of 45 months, which was like our previous study [10]. According to our findings in the current study, although the rate of patients in remission was slightly less in the group without mutation (69.8% vs. 76.5%), the difference was not significant.

In the study by Zhao et al., which comprised 33 C3GN, 10 DDD and 24 IC-mediated MPGN individuals, genetically diagnosed patients appeared to have better kidney survival than those without diagnoses [20]. In their study, the reason for better kidney survival in patients with mutation is not clarified. In another study, Iatropoulos et al. included 52 patients with C3GN, 21 DDD, and 67 IC-mediated MPGN and investigated if gene variations in alternative pathway of complement system and different patterns of complement activation associate with clinical presentation and outcomes. They found that patients without complement gene mutations have a higher risk of progression to CKD5 than patients with identified mutations and speculated that the presence of different pathogenetic mechanisms results in kidney disease [11]. In another study by Iatropoulos et al. [29] including 173 patients diagnosed with C3/IC-MPGN, patients were classified in 4 different clusters according to histologic, genetic, clinical, and serum plasma complement parameters. In clusters 1–3, C3 levels were low, and genetic and acquired abnormalities related to the alternative complement pathway were more common. In cluster 4, genetic mutations were significantly lower than the other groups with a rate of 4%. In the same study, although there was no difference between the clusters in terms of CKD5, there was a difference in terms of CKD that did not reach statistical significance [29].

Contrary to previous studies [11, 20, 29] we could not show any difference in kidney survival between patients with

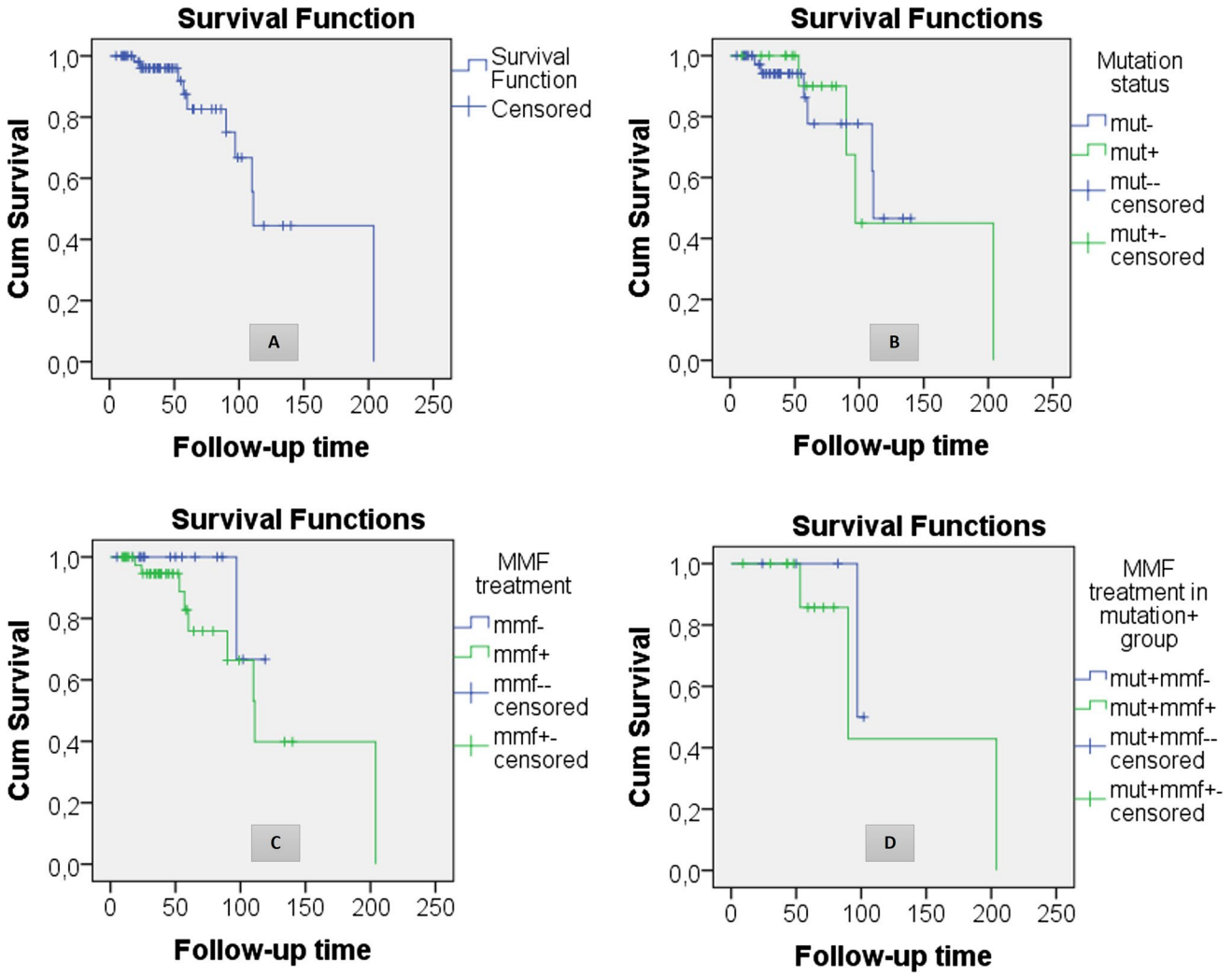


**Fig. 1** Kaplan–Meier analysis for CKD5. **A** In all study groups**.** Mean CKD5 development time in the study group 138.7 ± 17.4 (95% CI, 104.5–172.8). **B** In the group with and without mutation, mean CKD5 development time in the group with and without mutation 139.1 ± 30.5 and 110.4 ± 9.7 months, respectively ($p = 0.98$). **C** In the study group by MMF use status, mean CKD5 development time in the group with MMF use and non-use 130.9 ± 19.7 and 111.6 ± 5.9 months, respectively ($p = 0.282$). **D** In the group with mutations by MMF use status, mean CKD5 development time in the group with MMF use and non-use 133.5 ± 44.9 and 99.5 ± 1.76 months, respectively ($p = 0.572$)

and without mutations. Although patients from the pediatric age group were included in the previous studies, those studies predominantly included adult patients. In addition, the distribution of genetic mutations in our study is different from these studies [11, 20, 29]. The *CFB* mutation, the second most common mutation in our patients, was less common in these studies [11, 20] whereas the C3 mutation, which is more common in these studies, was less common in our cohort. This may have contributed to the different results in kidney survival between the studies. In addition, the fact that patients with mutation and/or C3NeF positivity were included in the same group in the study by Iatropoulos et al. may have contributed to the different results in their study [11]. Additional studies in different ethnic groups are needed to evaluate the clinical effects of complement mutations separately in both children and adults.

Although there are studies on the efficacy of MMF exposure in the treatment of C3 glomerulopathy [16, 27, 30], the number of studies investigating the efficacy of MMF in C3 glomerulopathy developed on a genetic basis is very few [17]. Caravaca-Fontán et al. [17] investigated whether corticosteroids plus MMF combination positively affects outcomes and disease progression in patients genetically diagnosed or having complement regulatory factors. They concluded that response to MMF treatment occurs regardless of genetic background or presence of antibodies. In line with this, in the present study, we found no difference in the effect of MMF treatment on kidney survival in patients with or

without mutations. In other words, even though the number of patients was small, in our study, it was shown that the use of MMF did not provide a statistically significant difference in kidney survival in genetically diagnosed cases.

The strengths of this study include the following: (1) data were collected from 18 pediatric nephrology centers from various cities in different regions; (2) it included patients in whom genetic factors that could cause C3G were investigated; and (3) it is the first multicenter pediatric study showing MMF treatment is unable to change kidney survival in both patients with and without complement gene mutations.

Our study also has limitations: (1) The fact that we could not obtain any information about serum levels of MMF is one of the limiting factors of this study. In addition, due to low albumin levels in the mutation group, MMF serum levels may have been lower than normal and may have affected the result. (2) We could not measure eculizumab free and bound C5 levels. This may be a limitation in the evaluation of treatment efficacy. (3) Kidney biopsy samples were evaluated by the local pathologist at the treating institution. Only one pathologist did not verify the diagnoses. (4) We could not study C3NeF and C5NeF in all patients because of the retrospective nature of this study (Fig. 1).

Despite all these limitations, we still think that this study might present valuable information for the guidance of C3G management in clinical practice for pediatric nephrologists.

In conclusion, in this study, we showed that our patients in the mutation group often presented with asymptomatic urinary abnormalities at the beginning and were diagnosed relatively late, but were not different from the without mutation group in terms of MMF treatment response and kidney survival. This showed a different result from other studies evaluating adult patients. We think that the impact of MMF treatment on the clinical course of pediatric C3G patients, regardless of genetic mutation, is limited. Although the detection of mutations by genetic studies is important in revealing the pathophysiology of the C3G disease, more studies are needed to understand its effect on prognosis. Especially when designing these studies, treatments should be well standardized and planned to evaluate adult- and pediatric-onset C3G patients separately.

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**Author contribution** NG, ID, and HMP designed the study. NG, ID, IG, MAK, DT, NÇ, MTB, MK, ND, HD, SS, ZNYY, SY, OD, SY, BDK, ÖA, BA, AÇY, SAB, MBA, MT, BKD, AS, EÇ, AKÖ, AK, NC, AY, IG, KBA, HA, and HMP carried out the recruitment of patients into the study. ID and NG analyzed, interpreted the data, and wrote the article. All the authors reviewed and revised the article and approved the final version.

**Data availability** Data for this study may be obtained by emailing the corresponding author.

## Declarations

**Competing interests** The authors declare no competing interests.

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