ChiKD CHILDHOOD KIDNEY DISEASES

Case Report

Child Kidney Dis 2024;28(3):124-130
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.24.015

C3 glomerulonephritis with genetically confirmed C3 deficiency in a pediatric patient: a case report

Hae Min Kim[1], Jae Il Shin[1,2,3], Ji Hong Kim[1,4], Jiyoung Oh[1,5], Ji-Man Kang[1,6], Hee Gyung Kang[7], Seong Heon Kim[7], Byoung Soo Cho[8], Keum Hwa Lee[1,2,3]

[1]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Division of Pediatric Nephrology, Severance Children's Hospital, Seoul, Republic of Korea
[3]Institute of Kidney Disease Research, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Pediatrics, Gangnam Severance Hospital, Seoul, Republic of Korea
[5]Department of Clinical Genetics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[6]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Republic of Korea
[7]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea
[8]Dr. Cho's Kidney Clinic, Seoul, Republic of Korea

Complement component 3 glomerulonephritis (C3GN) is a rare kidney disease characterized by complement dysregulation that results in prominent complement component 3 (C3) deposition in the kidneys. The clinical course of C3GN varies from mild hematuria to progressive chronic kidney disease. In most patients, C3GN is driven by acquired factors, namely, autoantibodies that target C3 or C5 convertases. Genetic variations in complement-related genes are less frequent. We report the case of a 9-year-old Korean boy who presented with microscopic hematuria and a persistently low C3 level and had biopsy findings of C3GN, with the presence of a *C3* gene mutation: a frameshift mutation associated with C3 deficiency. However, the patient did not exhibit any other symptoms of complement deficiency. Direct DNA sequencing of his family members revealed the same genetic mutation in his father and older brother. This case report is significant because there are very few such reports worldwide concerning gene mutations related to C3 deficiency to be discovered in patients with C3GN. Explaining C3GN pathogenesis is challenging; therefore, additional research is required in the future.

Keywords: Case reports; Complement component 3 deficiency; Glomerulonephritis

Introduction

Complement component 3 glomerulonephritis (C3GN) is a rare disease in which complement component 3 (C3) is deposited without immunoglobulin deposition in the glomeruli of the kidney due to dysregulation of the alternative complement pathway [1]. Most C3GNs appear as membranous and membranous proliferative glomerulonephritis (GN) patterns under light microscopy [2]. Clinical manifestations of C3GN include typical signs of GN, hypertension in asymptomatic microscopic hematuria, proteinuria and may be accompanied by renal dysfunction, which may later progress to chronic renal failure [3].

In most patients, C3 glomerulopathy—which includes dense deposit disease (DDD) and C3GN—is caused by acquired fac-

Received: September 13, 2024; Revised: October 3, 2024; Accepted: October 14, 2024

Correspondence to
Keum Hwa Lee
Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
E-mail: azsagm@yuhs.ac

tors, such as autoantibodies to various complement proteins and complexes. However, in about 25% of cases, C3 glomerulopathy results from genetic factors, including mutations related to the complement system [4]. Genes associated with C3GN include *C3*, complement factor B (*CFB*), complement factor H (*CFH*), complement factor I (*CFI*), and complement factor H-related 5 (*CFHR5*) genes (Table 1) [5]. While many mutations have been previously reported in C3GN, the significance of some of these mutations and the pathogenesis of C3GN are not yet well known [6].

C3 plays a central role in activating both the classical and alternative complement pathways [1]. Congenital complement deficiency usually occurs in an autosomal recessive inheritance mode and is a rare disease with a prevalence of 0.03% except for mannose-binding lectin (MBL) deficiency, which occurs in 5% of Caucasians [7]. The most common congenital complement deficiencies involve C2 and MBL deficiencies (Table 1) [7]. Because clinical manifestations of complement deficiency vary from asymptomatic to life-threatening infectious and autoimmune diseases, accurate medical history and examination of the entire family are important [7]. However, to our knowledge, clinical manifestations of C3 deficiency in the form of C3GN have not yet been reported.

Here, we report the case of a 9-year-old Korean boy with confirmed C3GN and a *C3* gene mutation associated with C3 deficiency. He was diagnosed with C3GN after renal biopsy, underwent genetic testing to investigate gene mutations causing renal diseases, and was confirmed to have a heterozygous frameshift mutation in the *C3* gene, which causes C3 deficiency. Therefore, the patient was diagnosed with two rare diseases: C3 deficiency and C3GN. In this case, the same *C3* gene mutation was also confirmed in the father and older brother. We aimed to understand the pathogenesis of this patient who simultaneously had these two diseases, the pathogenesis of which remains unknown.

Case report

The patient was found to have microscopic hematuria during a school check-up when he was 9 years old. He was suspected of having an acute post-streptococcal glomerulonephritis at another hospital and was followed up; however, his complement levels were consistently low. Therefore, he visited the outpatient clinic on November 30, 2018. In initial laboratory test results, isolated depression of C3 at 24.4 mg/dL (reference range, 90–180 mg/dL) was noted; however, with normal C4 levels at 18.5 mg/dL (reference range, 10–40 mg/dL). By urinalysis, microscopic hematuria (urine blood 1+, number of red blood cells: 29/μL); however, no proteinuria was observed. No remarkable findings were observed on kidney ultrasonography. However, at regular follow-up, he developed proteinuria in July 2019. Therefore, we recommended a renal biopsy and genetic study; however, the parents refused. As a result, he was prescribed prednisolone (Solondo, Yuhan Medica Corp.) at a dosage of 1 mg/kg administered in divided doses three times daily. However, due to gastrointestinal side effects, tapering of prednisolone commenced on July 25, 2019. On November 21, 2019, the patient initiated treatment with angiotension receptor antagonist containing the ingredient losartan (Cozaar, Merck Sharp & Dohme Ltd.) at a dose of 25 mg once daily, which was subsequently increased to 50 mg once daily on January 16, 2020. On April 25, 2020, persistent proteinuria prompted the initiation of cyclosporine (Cipol, Chong Kun Dang Pharm.) at a dosage of 25 mg twice daily. However, by November 14, 2020, the patient exhibited cognitive decline, dizziness, and depression, resulting in the discontinuation of cyclosporine and a reduction of losartan to 25 mg once daily. On January 23, 2021, due to worsening proteinuria, the dose of losartan was increased to 50 mg once daily (Fig. 1). However, proteinuria was persistent and C3 levels did not recover even after several months and remained very low (<2 mg/dL), supporting the presence of a complement-me-

Table 1. Known gene mutation in C3GN and complement deficiency [4,5,7]

Diseases	Known gene mutation
C3GN	*Factor H, factor I, C3*[a], *factor B, MCP, THBD, DGKE, plasminogen*
Complement deficiency	Components: *C1q, C1r, C1s, C4 (C4A, C4B), C2, C3*[a], *C5, C5, C6, C7, C8, C9, factor B, factor D, MBL, ficolin-3, MASP-2, MASP-3, CL-K1, CL-L1*
	Regulators: *C1-inhibitor, C4-binding protein, properdin, factor H, FHR1, factor I, CD46/MCP, CD55/DAF, CD59*
	Receptors: *CR3 (CD18/CD11b), CR4 (CD19/CD11c, LFA-1)*

C3GN, complement component 3 glomerulonephritis; MCP, membrane cofactor protein; THBD, thrombomodulin; DGKE, diacylglycerol kinase epsilon; MBL, mannose-binding lectin; MASP, mannose-binding protein-associated serine protease; CL-K1, collectin kidney 1; CL-L1, collectin liver 1; FHR1, factor H-related protein 1; DAF, decay-accelerating factor; LFA-1, lymphocyte function-associated antigen 1.
[a]The gene mutation in this patient case.

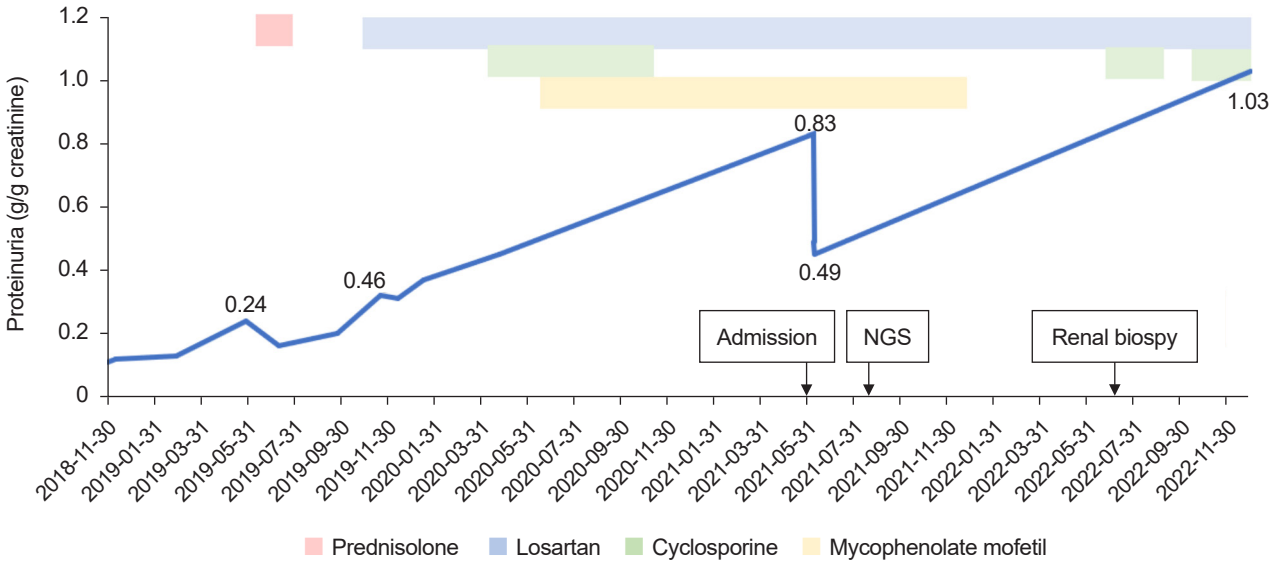

Fig. 1. Clinical course of treatment to the patient. NGS, next-generation sequencing.

Table 2. Next-generation sequencing result for a renal disease gene panel

Gene	Nucleotide	Amino acid	Genotype	ACMG classification
C3	NM_000064.2:c.1005_1015delCAGTGACATGG	NP_000055.2:p.Ser336AlafsTer32	het	Likely pathogenic
PKD1	NM_001009944.2:c.242C>T	NP_001009944.2:p.Ala81Val	het	Uncertain significance
FBN2	NM_001999.3:c.6757+2C>T	-	het	Likely pathogenic
MFAP5	NM_003480.2:c.472C>T	NP_003471.1:p.Arg158Ter	het	Pathogenic

ACMG; American College of Medical Genetics and Genomics; C3, complement component 3; PKD1, polycystic kidney disease 1; FBN2, fibrillin 2; MFAP5, microfibril-associated protein 5; het, heterozygous.

diated disorder. On June 9, 2021, he was hospitalized because of weight loss of 4 kg in 1 month, vomiting, abdominal pain, and increased proteinuria. At that time, he was diagnosed with pancreatitis; therefore, conservative treatment was administered and high-dose steroid therapy was not administered. After the event, the parents agreed to the genetic study; therefore, we conducted next-generation sequencing (NGS) for a renal disease gene panel on August 18, 2021. NGS results revealed variants of the *C3*, fibrillin 2 (*FBN2*), and microfibril-associated protein 5 (*MFAP5*) genes (Table 2). The *C3* gene provides instructions for the creation of a protein called C3 [8]. C3 protein is essential for activating the complement system [8]. Some mutations in *C3* have been found to cause C3GN and some mutations in the *C3* gene have been found to cause C3 deficiency [7,9]. *MFAP5* is a protein-coding gene. Diseases associated with *MFAP5* mutations include aortic aneurysms and aortic dissection [10,11]. *FBN2* is a protein-coding gene. Diseases associated with *FBN2* include contractural arachnodactyly, and congenital early-onset macular degeneration [12]. This patient had no other clinical symptoms associated with *MFAP5* and *FBN2* gene mutations. To date, he has exhibited no symptoms, such as recurrent bacterial infections typically seen in C3 deficiency. Since C3-deficient patients are vulnerable to encapsulated bacteria, he was vaccinated against pneumococcal infection and continued treatment for GN. After consultation with the Pediatric Cardiology Department regarding the *MFAP5* mutation, the Ophthalmology Department and the Clinical Genetics Department for the *FBN2* mutation, and the Pediatric Infectious Disease and Immunology Department for the *C3* mutation, no other abnormalities were noted. However, since symptoms might develop in the future, we decided to conduct follow-up observations involving the four departments. After NGS, owing to prolonged proteinuria and hypocomplementemia, the boy's parents agreed to a kidney biopsy performed on June 30, 2022. The biopsy result was C3GN with features of diffuse proliferative GN (Fig. 2). The glomeruli were moderately sized and hypercellular, involving

https://doi.org/10.3339/ckd.24.015

endocapillary cells. Mesangial interposition, forming a double contour, was occasionally observed. One glomerular sample (8%) showed segmental sclerosis. Ultrastructural examination disclosed heavy mesangial deposits and large, scattered subepithelial "humps" as with localized subendothelial deposits. Mesangial interpositions were rarely observed. The epithelial cell foot processes exhibited marked focal effacement. The main immunofluorescence findings were prominent and diffuse C3 deposits, granular and nodular in some glomerular areas. Therefore, the patient was diagnosed as having C3GN. Due to persistent proteinuria, on June 12, 2021, mycophenolate mofetil (Myrept, Chong Kun Dang Pharm.) was initiated at a dosage of 250 mg twice daily, which was subsequently increased to 500 mg twice daily on June 22, 2021. However, due to the development of a skin rash on August 18, 2021, the dosage was reduced back to 250 mg twice daily. A follow-up esophagogastroduodenoscopy conducted on December 20, 2021, revealed persistent gastric and duodenal ulcers, necessitating a further reduction in mycophenolate mofetil. On July 18, 2022, the dosage of losartan was reduced to 25 mg once daily due to dizziness, and cyclosporine was re-initiated at 25 mg once daily. On August 17, 2022, due to persistent proteinuria, the dosage of cyclosporine was increased to 25 mg twice daily; however, the patient subsequently experienced dizziness and delirium, leading to the discontinuation of cyclosporine on August 27, 2022. Following a further exacerbation of proteinuria, cyclosporine was reintroduced at a dosage of 25 mg every other day on November 12, 2022 (Fig. 1). Currently, the patient has normal kidney function; however, proteinuria and hematuria still persist. His family members underwent direct gene sequencing for the patient's mutations (*C3*, *PKD1*, *FBN2*, and *MFAP5*). In the father, heterozygous mutations in *C3* and *FBN2* were confirmed. In the mother, heterozygous mutations in *PKD1* and *MFAP5* were confirmed. In the patient's older brother, a heterozygous mutation involving

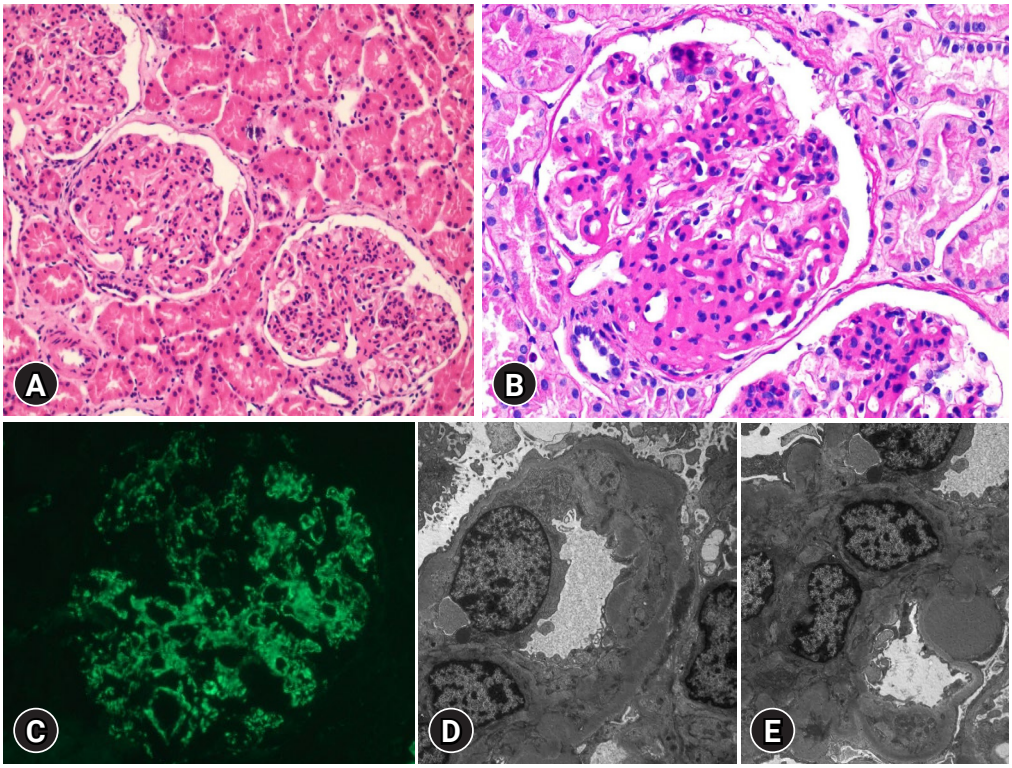

Fig. 2. Light microscopy, immunofluorescence, and electron microscopy findings. (A) Hematoxylin and eosin stain (×200). (B) Periodic Acid-Schiff stain (×400). The glomeruli are of moderately increased size and moderately hypercellular involving endocapillary cells. Mesangial interposition is occasionally seen, forming double contours. One glomerulus (8%) exhibits segmental sclerosis. Tubules reveal focal slight atrophy and loss with interstitial fibrosis. (C) Immunofluorescence (×200). Diffuse C3 deposits in the mesangium and glomerular capillary walls (IgG negative, IgM negative, IgA negative, C3+ diffuse granular peripheral and mesangial staining, C1q negative, C4 negative, fibrinogen 1+ diffuse granular peripheral staining, Kappa negative, Lamda negative). (D, E) Electron microscopy (×5,000). Heavy mesangial deposits and scattered big subepithelial "humps" as with localized subendothelial deposits. Mesangial interposition is rarely seen. Epithelial cell foot processes show focal marked effacement.

Table 3. Gene mutation in the patient and his family

Gene	Mutation	Patient	Father	Mother	Older brother	Younger sister
C3	NP_000055.2:p.Ser336AlagsTer32	O (het)	O (het)	X	O (het)	X
PKD1	NP_001009944.2:p.Ala81Val	O (het)	X	O (het)	X	O (het)
FBN2	NM_001999.3:c.6757+2C>T	O (het)	O (het)	X	X	X
MFAP5	NP_003471.1:p.Arg158Ter	O (het)	X	O (het)	X	X

C3, complement component 3; PKD1, polycystic kidney disease 1; FBN2, fibrillin 2; MFAP5, microfibril-associated protein 5; het, heterozygous.

the *C3* gene was confirmed. A heterozygous mutation in the *PKD1* gene was also confirmed (Table 3). His parents and younger sister were in good health and the older brother had only microscopic hematuria and no proteinuria. Blood examination of family members revealed serum C3 levels of 55.2 mg/dL in the father, 57.6 mg/dL in the older brother, and normal levels in the sister. Serum CH50 and C4 levels in the father, older brother, and sister were all within the normal ranges. Since the patient's older brother also had the *C3* gene mutation, microscopic hematuria, and low C3 levels, he was followed up with close monitoring of nephritic symptoms and planning for further evaluation for GN treatment.

Discussion

In our case, a 9-year-old Korean boy with prolonged microscopic hematuria, proteinuria, and low C3 levels was pathologically confirmed to have C3GN by renal biopsy and diagnosed with C3 deficiency in the presence of a *C3* gene mutation. However, the patient never experienced recurrent bacterial infections, which is a typical clinical symptom of C3 deficiency.

We were curious whether there were any other cases of *C3* mutations without C3 deficiency symptoms. A previous study reported some cases with a *C3* mutation that had mild or no symptoms of infection. In a study by Okura et al. [13], patients with *C3* mutations in the N-terminal half of the gene tended to be more susceptible to severe infections, whereas patients without severe infections had *C3* mutations that were concentrated downstream of the thioester domain (TED) [13]. Although the biological function of mutant C3 molecules has not yet been determined, we hypothesized that the hereditary *C3* mutation in our patient may have occurred downstream of the TED in the *C3* gene. This may explain why our patient did not exhibit any symptoms of infection. To address this possibility, developing a novel quantitative and functional assay to identify mutant C3 molecules is necessary. Other hypotheses may also exist. Almost all cases of C3 deficiency have been reported as homozygous mutations involving *C3* and no functional mature C3 molecule can be produced [14]. Some compound heterozygous mutations can be compensated for by binding of the remaining wild type and the functionally normal α and β chains from the different alleles to avoid more severe C3 deficiency [14]. This hypothesis is consistent with the unexpected finding of hereditary C3 deficiency. To address this possibility and to identify other mutations, whole-genome sequencing (WGS) appears to be the best choice. In the future, when WGS of national bio-big data is possible, our patient and his parents need to search for heterozygous or autosomal recessive mutations using WGS. Subsequently, demonstrating the candidate gene in knockout mice, confirming the mutation in the older brother, and performing a renal biopsy, if needed, are necessary. Interestingly, the father and older brother also shared the same *C3* mutation, but their C3 levels and symptoms differed from those of the patient. Serum C3 levels were 24.4, 55.2, and 57.6 mg/dL in the patient, father, and older brother, respectively. Although the patient had proteinuria and microscopic hematuria, his father had no such symptoms, and his older brother had intermittent microscopic hematuria. Even though his brother did not undergo kidney biopsy, C3GN was strongly suspected. This may be due to differences in disease penetrance. In addition, in this patient's case, not only the *C3* mutation but also other gene mutations (*PKD1*, *FBN2*, and *MFAP5*) were discovered. There are currently no reports of cases in which these mutations were discovered together, as far as we can identify. No clinical symptoms have occurred due to the above gene mutations in the patient and his family; however, they are being followed up.

Similar to how the clinical manifestations of other gene mutations may not correspond with those observed in this patient, *C3* mutations may also present with distinct clinical profiles. However, considering the following hypothesis, we could suggest that *C3* mutations may be associated with C3GN. It is very questionable as to how *C3* mutation can cause C3GN in which C3 is deposited since C3 deficiency is a genetic condition in which C3 is produced at low or no level. In a paper by Marti-

https://doi.org/10.3339/ckd.24.015

nez-Barricarte et al. [8], the authors identified a unique DDD pedigree that associated disease with a mutation in the *C3* gene. Mutant C3923ΔDG which lacks two amino acids, could not be cleaved to C3b by the C3-convertase and was therefore the predominant circulating C3 protein in the patients [8]. This genetic change is described as a "gain-of-function" mutation because it leads to an altered version of the protein that overactivates the complement system [14]. An overactive system damages glomeruli. We suggest the possibility that the *C3* mutation in our patient can also cause "gain-of-function." This possibility should be explored in future studies. One limitation of our study is that we only measured, C3 and C4 levels in our patient. Since the cause is dysregulation of the alternative complement pathway, serum C3 levels as well as CFH, CFI, and CFB must be measured, and C3 nephritic factor and anti-factor H autoantibodies must be investigated [1]. To evaluate the patient's acquired etiologies for C3GN, it would have been better to measure CFH, CFI, and CFB and test for C3 nephritic factor and anti-factor H antibodies. Unfortunately, the hospital did not have the corresponding test.

Because the patient and guardian initially refused genetic and renal tissue testing, the patient was treated with steroids and immunosuppressants for 4 years. When they became ineffective, genetic and kidney tissue testing was performed relatively late. As a general guideline, in cases where persistent hypocomplementemia and renal symptoms are present but no evidence of immune deficiency is noted, a kidney biopsy should be prioritized. However, in cases like our patient, where the patient's guardian declines the biopsy, or if there is a suspicion of immune deficiency, or if complement levels are markedly reduced to the extent, it is advisable to consider genetic testing. Due to the side effects of steroids and immunosuppressants, we could only use symptomatic treatments such as angiotensin converting enzyme antagonists. We also considered the possibility of eculizumab, which acts on the C3 complement system, as a treatment; however, because the mechanism is not yet clearly understood, predicting the effects and side effects of eculizumab is challenging [15]. In addition, a trial involving eculizumab was difficult due to cost issues.

In our patient's case, a *C3* gene mutation was discovered in C3GN; in particular, the same gene mutation was found in his father and older brother. This represents a unique form of complement system deficiency called C3 deficiency; however, the patient and his family members did not have recurrent infection symptoms. In addition to the *C3* mutation, other gene mutations related to aortic aneurysms, contractural arachnodactyly, and congenital macular degeneration were detected in this patient. But the patient did not present with any of these symptoms. To our knowledge, this case report is meaningful because there are very few case reports worldwide of both C3GN and C3 deficiency. There are many questions left to be answered regarding its pathogenesis, and additional research will be needed in the future.

Ethical statements

This study was approved by the Institutional Review Board (IRB) and Research Ethics Committee of Yonsei University Severance Hospital (IRB No. 4-2023-09454). We were exempted from obtaining informed consent from the IRB because the study was retrospective, personal identifiers were completely removed, and the data were analyzed anonymously.

Conflicts of interest

Jae Il Shin, Hee Gyung Kang and Keum Hwa Lee are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

Conceptualization: KHL
Data curation: HMK
Formal analysis: HMK, JO
Investigation: HMK
Methodology: JIS, JO, JMK, KHL
Project administration: JHK, HGK, SHK, BSC
Visualization: HMK, KHL
Writing–original draft: HMK
Writing–review & editing: HMK, JIS, JHK, JO, JMK, HGK, SHK, BSC, KHL
All authors read and approved the final manuscript.

References

1. Kim YJ. Pathology of C3 glomerulonephritis. J Korean Soc Pediatr Nephrol 2013;17:1-5.
2. Appel GB. C3 glomerulopathy: a new disease comes of age. Mayo Clin Proc 2018;93:968-9.
3. Sethi S, Fervenza FC, Zhang Y, Zand L, Vrana JA, Nasr SH, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney Int 2012;82:465-73.
4. Smith RJH, Appel GB, Blom AM, Cook HT, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy: understanding a rare complement-driven renal disease. Nat Rev Nephrol 2019;15:129-43.
5. Servais A, Noel LH, Fremeaux-Bacchi V, Lesavre P. C3 glomerulopathy. Contrib Nephrol 2013;181:185-93.
6. Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S. C3 glomerulopathy: ten years' experience at Mayo Clinic. Mayo Clin Proc 2018;93:991-1008.
7. Schroder-Braunstein J, Kirschfink M. Complement deficiencies and dysregulation: Pathophysiological consequences, modern analysis, and clinical management. Mol Immunol 2019;114:299-311.
8. Martinez-Barricarte R, Heurich M, Valdes-Canedo F, Vazquez-Martul E, Torreira E, Montes T, et al. Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. J Clin Invest 2010;120:3702-12.
9. Xiao X, Pickering MC, Smith RJ. C3 glomerulopathy: the genetic and clinical findings in dense deposit disease and C3 glomerulonephritis. Semin Thromb Hemost 2014;40:465-71.
10. Barbier M, Gross MS, Aubart M, Hanna N, Kessler K, Guo DC, et al. MFAP5 loss-of-function mutations underscore the involvement of matrix alteration in the pathogenesis of familial thoracic aortic aneurysms and dissections. Am J Hum Genet 2014;95:736-43.
11. Li Y, Kong Y, Duan W, Yu S, Zhou X, Hu Y, et al. Evaluating the monogenic contribution and genotype-phenotype correlation in patients with isolated thoracic aortic aneurysm. Eur J Hum Genet 2021;29:1129-38.
12. Zhang H, Apfelroth SD, Hu W, Davis EC, Sanguineti C, Bonadio J, et al. Structure and expression of fibrillin-2, a novel microfibrillar component preferentially located in elastic matrices. J Cell Biol 1994;124:855-63.
13. Okura Y, Kobayashi I, Yamada M, Sasaki S, Yamada Y, Kamioka I, et al. Clinical characteristics and genotype-phenotype correlations in C3 deficiency. J Allergy Clin Immunol 2016;137:640-4.
14. Kida M, Fujioka H, Kosaka Y, Hayashi K, Sakiyama Y, Ariga T. The first confirmed case with C3 deficiency caused by compound heterozygous mutations in the C3 gene; a new aspect of pathogenesis for C3 deficiency. Blood Cells Mol Dis 2008;40:410-3.
15. Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol 2012;7:748-56.

https://doi.org/10.3339/ckd.24.015