Tohoku J. Exp. Med., 2022, **258**, 183-193

An Infant Case of *Streptococcus Pneumoniae*-Associated Thrombotic Microangiopathy with Heterozygous *CFI* Mutation and *CFHR3-CFHR1* Deletion

Yuji Matsumoto,[1] Yohei Ikezumi,[1] Tomomi Kondoh,[1] Katsuyuki Yokoi,[1] Yoko Nakajima,[1] Naonori Kumagai,[1] Takema Kato,[2] Hiroki Kurahashi[2] and Tetsuya Ito[1]

[1]Department of Pediatrics, Fujita Health University School of Medicine, Toyoake, Aichi, Japan
[2]Division of Molecular Genetics, Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Aichi, Japan

Thrombotic microangiopathy (TMA) is a disease that causes organ damage due to microvascular hemolytic anemia, thrombocytopenia, and microvascular platelet thrombosis. *Streptococcus pneumoniae*-associated TMA (spTMA) is a rare complication of invasive pneumococcal infection. In addition, atypical hemolytic uremic syndrome (aHUS) is TMA associated with congenital or acquired dysregulation of complement activation. We report the case of a nine-month-old boy with refractory nephrotic syndrome complicated by spTMA in the setting of heterozygous complement factor-I (*CFI*) gene mutation and *CFHR3-CFHR1* deletion. He repeatedly developed thrombocytopenia, anemia with schistocytes, hypocomplementemia, and abnormal coagulation triggered by infection, which manifested clinically with convulsions and an intraperitoneal hematoma. Eculizumab (a monoclonal humanized anti-C5 antibody) provided transient symptomatic benefit including improvement in thrombocytopenia; however, he developed unexplained cardiac arrest and was declared brain dead a few days later. In this report, we highlight the diagnostic challenges of this case and the causal relationship between spTMA and complement abnormalities and consider the contribution of heterozygous mutation of *CFI* and *CFHR3-CFHR1* deletion.

Keywords: atypical hemolytic uremic syndrome; complement factor H-related gene; complement factor I; infantile nephrotic syndrome; pneumococcal infection
Tohoku J. Exp. Med., 2022 November, **258** (3), 183-193.
doi: 10.1620/tjem.2022.J076

Introduction

Thrombotic microangiopathy (TMA) is a disease that causes organ damage due to microvascular hemolytic anemia, thrombocytopenia, and microvascular platelet thrombosis. TMA predominantly affects the renal microvasculature but may also present with extrarenal manifestations involving the central nervous system, respiratory system, cardiovascular system, and gastrointestinal tract (Hofer et al. 2014).

The frequent causes of TMAs are hemolytic uremic syndrome (HUS) associated with Shiga-toxin-producing *Escherichia coli* infection and thrombotic thrombocytopenic purpura (TTP) mediated by ADAMTS13 deficiency (Jokiranta 2017). Secondary TMA is defined as TMA arising from other infectious diseases, drugs, pregnancy, transplantation, metabolic disorders, autoimmune diseases, and other causes (Kato et al. 2016). *Streptococcus pneumoniae*-associated TMA (spTMA) is a representative of secondary TMA due to infectious disease. The clinical course is severe and no specific treatment for spTMA has been established (Scobell et al. 2020).

Atypical HUS (aHUS) is considered as a complement-mediated TMA associated with congenital or acquired dysregulation of complement activation. Congenital genetic abnormalities associated with aHUS include the pathogenic variants of genes encoding complement factor H (CFH), factor I (CFI), factor B, membrane cofactor protein, C3,

Received June 10, 2022; revised and accepted August 28, 2022; J-STAGE Advance online publication September 8, 2022
Correspondence: Yuji Matsumoto, Department of Pediatrics, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan.
e-mail: ymatsumo@fujita-hu.ac.jp

thrombomodulin, and diacylglycerol kinase epsilon (DGKE). Acquired aHUS with anti-CFH antibody has also been identified (Kato et al. 2016; Jokiranta 2017). Eculizumab, a monoclonal humanized anti-C5 antibody, is known to be effective in the treatment of aHUS (Legendre et al. 2013). Although aHUS is diagnosed when secondary TMA is ruled out, complement-related genetic abnormalities may also be present in secondary TMA, including spTMA (Szilágyi et al. 2013; Brocklebank et al. 2018; Yoshida et al. 2019). In addition, infection and other diseases may also precede the onset of aHUS (Jokiranta 2017), and it is sometimes difficult to distinguish between aHUS and secondary TMA clinically.

Nephrotic syndrome (NS) is one of the most common childhood kidney diseases and is rare in the first year of life. Most infantile NS patients have genetic abnormalities, and most of them have a poor response to steroid treatment and develop end-stage renal failure (Hinkes et al. 2007). In NS patients, there is a risk of infectious diseases, especially peritonitis and sepsis due to *Streptococcus pneumoniae* (Malaker et al. 2019).

Here, we report an infant with spTMA and refractory NS with various complications associated with complement dysregulation.

Case Presentation

The patient was a previously healthy nine-month-old Japanese boy who developed edema shortly after being diagnosed with respiratory syncytial virus (RSV) infection by his family doctor approximately 10 days before admission to our hospital. The patient had a temperature of 39°C the day before admission. He presented with marked edema, peripheral cyanosis, facial pallor, and tachypnea (respiratory rate of 36/min) and was admitted to our hospital. He had no external malformations including microcephaly and facial or limb malformations. Investigations revealed heavy proteinuria (urinary protein 7,552 mg/dL, 6.62 g/day), hypoproteinemia (albumin 0.2 g/dL), leukocytosis (41,600/μL), and an elevated C-reactive protein (CRP) level (13.03 mg/dL). Cerebrospinal fluid (CSF) examination showed no pleocytosis and CSF culture was negative; however, blood culture detected *Streptococcus pneumoniae,* and the patient was diagnosed with NS with sepsis. Treatment with prednisolone, albumin, furosemide, and cefotaxime was initiated. Subsequently, he became afebrile, and his white blood cell count and CRP levels improved; however, the severe edema persisted. On the 7th day of hospitalization, he had a generalized tonic-clonic convulsion, and brain magnetic resonance imaging (MRI) showed bilateral symmetric areas of increased intensity in the basal ganglia on T2 and diffusion-weighted imaging (Fig. 1A). Blood pressure was in the normal range (84/55 mmHg), and MRI findings were not typical of posterior reversible encephalopathy syndrome. Magnetic resonance spectroscopy showed no lactate elevation in the basal ganglia, and the blood lactate level was normal. Based on these results, we concluded that mitochondrial disease was unlikely to have caused the nephropathy and basal ganglia lesions. Further, there were no other risk factors of basal ganglia lesions including hypoxia, hypoglycemia, or vitamin deficiency. Around this time, the lactate dehydrogenase (LDH) and creatinine (Cr) levels increased (peak levels: LDH 535 IU/L, Cr 0.55 mg/dL on day 7), and the platelet counts began to decrease on day 8. Blood tests were repeated on the 10th day to monitor the patient's clinical course, and these revealed thrombocytopenia (platelets 30,000/μL), anemia (hemoglobin 8.4 g/dL) with schistocytes, decreased haptoglobin (4.0 mg/dL), hypocomplementemia (C3 19 mg/dL, reference range 86-160 mg/dL; C4 7 mg/dL, reference range 17-45 mg/dL; CH50 < 14.0/mL, reference range 28.0-38.0), abnormal coagulation with prothrombin time (PT)-ratio 1.60, antithrombin (AT) III 17%, fibrinogen < 35 mg/dL, fibrinogen/fibrin degradation products (FDP) 44.1 μg/mL, and elevated D-dimer (42.8 μg/mL), suggesting the development of secondary TMA due to *Streptococcus pneumoniae*; however, the direct Coombs test was negative. The data also suggested the development of disseminated intravascular coagulation (DIC), although the plasmin-alpha2-plasmin inhibitor-complex and thrombin-antithrombin complex were within the normal range (< 0.5 μg/mL, reference range < 0.8 μg/mL; and 1.8 ng/mL, reference range < 3.0 ng/mL, respectively). As these abnormal laboratory findings persisted and progressed, fresh frozen plasma, platelet, and antithrombin transfusions were repeatedly administered; however, the effects were limited. Since the NS was also resistant to steroid treatment, methylprednisolone pulse therapy and cyclosporine were initiated on the 17th day of admission; however, his heavy proteinuria and edema persisted.

Around the 30th day of admission, the patient developed upper abdominal distension, which was not consistent with ascites, and computed tomography (CT) examination revealed a huge hematoma in the omental bursa (Fig. 2). There was no evidence of thrombosis. Angiography revealed bleeding in the gastroepiploic artery, and on day 32, an emergency hematoma resection and kidney biopsy were performed simultaneously. Laboratory findings at this time were consistent with TMA and showed thrombocytopenia and hemolytic anemia with schistocytes, renal impairment, abnormal coagulation and fibrinolysis, and a decrease in complement. ADAMTS13 levels were within the normal range (126%). Kidney biopsy revealed immature glomeruli with focal sclerotic lesions and an edematous tubulointerstitial area with diffuse expanded tubules (Fig. 3A-D). There were no findings suggestive of membranous proliferative glomerulonephritis (MPGN), including glomerular cell proliferation and double contours of the basement membrane. Immunofluorescence staining showed diffuse deposition of C3 and fibrinogen in the interstitial area (Fig. 3E, F); however, no immunoglobulin was present in both glomerular and interstitial compartments. Although there were no obvious findings suggestive of TMA in the renal tissue such

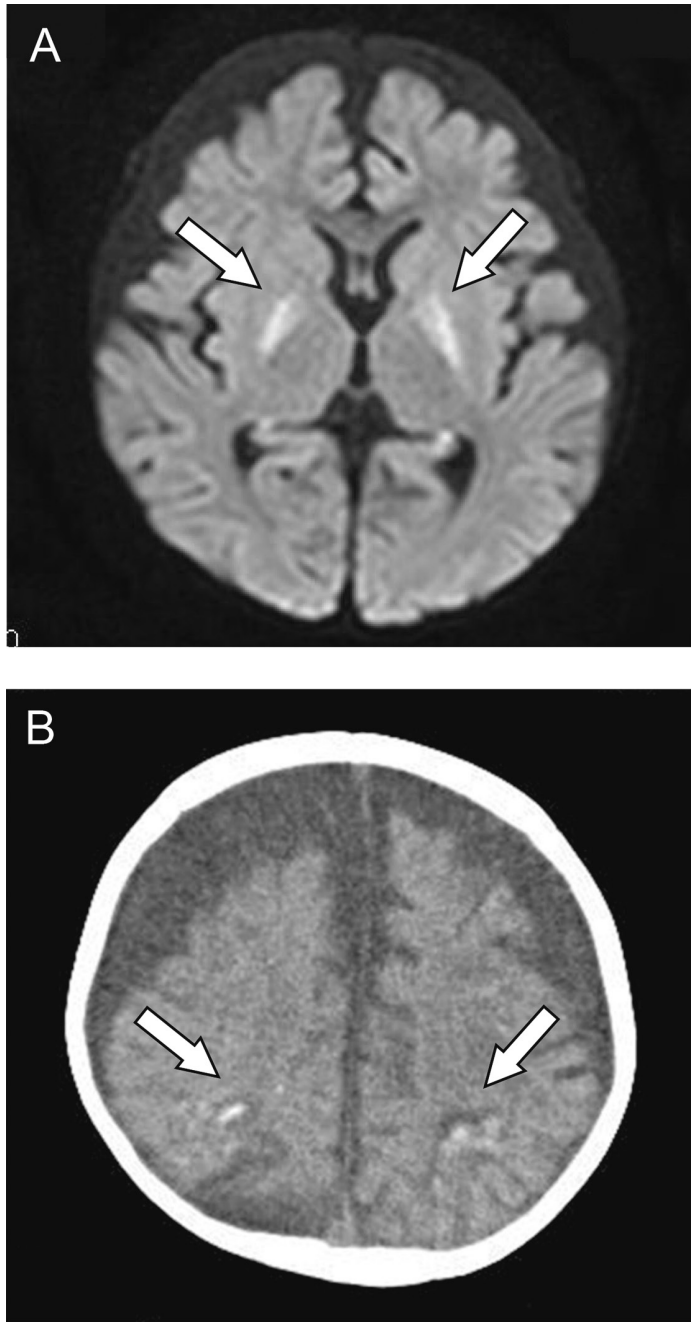

Fig. 1. Magnetic resonance imaging (MRI) and computed tomography (CT) of the brain.
A: On day 7, diffusion-weighted MRI of the brain showed increased signal intensity in the basal ganglia bilaterally (white arrow) and brain atrophy. B: On day 49, a head CT scan showed multiple cerebral parenchymal microhemorrhages in the parietal lobe (white arrow).

as vascular injury or thrombus, primary focal segmental glomerular sclerosis with complement-related disease was suspected. Due to persistent coagulation abnormalities, severe proteinuria, and renal dysfunction, we decided to commence eculizumab treatment on day 35. After initiation of eculizumab treatment, his renal function, platelet count, and complement levels improved (Cr 0.92 mg/dL, platelets 82,000/μL, and C3 52 mg/dL on day 34; and Cr 0.34 mg/dL, platelets 278,000/μL, and C3 83 mg/dL on day 42). However, on day 49, he developed fever, tonic-clonic convulsion, and unexplained cardiac arrest and was resuscitated. A CT performed immediately after resuscitation revealed multiple intracerebral microhemorrhages, which could have caused the cardiac arrest (Fig. 1B). The CT findings did not show pulmonary thrombosis. At that time, although blood test showed leukocytosis probably due to convulsion, there was no evidence of bacterial infection such as elevated CRP or positive blood culture. He was

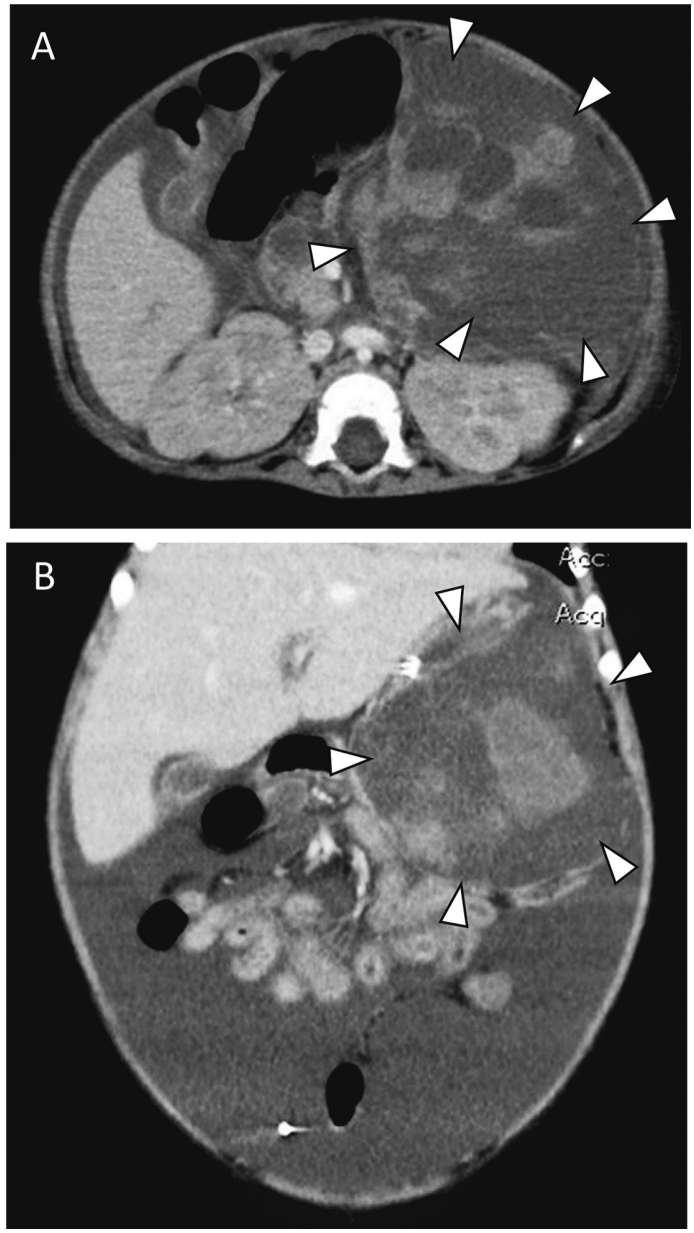

Fig. 2. Abdominal contrast-enhanced CT scan.
A huge hematoma is observed in the omental bursa (arrowhead). The high- and low-density areas were mixed, and part of the high-density area appeared after contrast, suggesting extravasations.

declared brain dead a few days later.

Complement analysis related to aHUS performed in this patient showed negative anti-factor H antibody titer (< 3.9 AU/mL, serum on the second day of admission), and genetic analysis by the target exome sequencing (Table 1) revealed a heterozygous missense mutation of c.603A>C (p. R201S) in *CFI* exon 4. Sanger sequencing of *CFI* exon 4 revealed that the patient's father, but not his mother, had the same variant (Fig. 4). In addition, analysis by the eXome Hidden Markov Model and the multiplex ligation-dependent probe amplification (MLPA) method revealed a *CFHR3-CFHR1* heterozygous deletion in the patient and his father (Fig. 5). His father had no remarkable past medical history. By contrast, no genetic abnormalities associated with congenital NS including those accompanied with a neurological disorder were identified by target exome sequencing (Table 1).

Informed consent was obtained from the parents of the patient for this case report. For the genetic analysis, ethics approval was obtained from the Ethics Committee of Fujita Health University for the study (number HG12-004), and written informed consent was obtained from the parents of the patient.

Discussion

This report describes an unusual case of infantile NS with spTMA, resulting in convulsion, intra-abdominal hematoma, and intracerebral microhemorrhage.

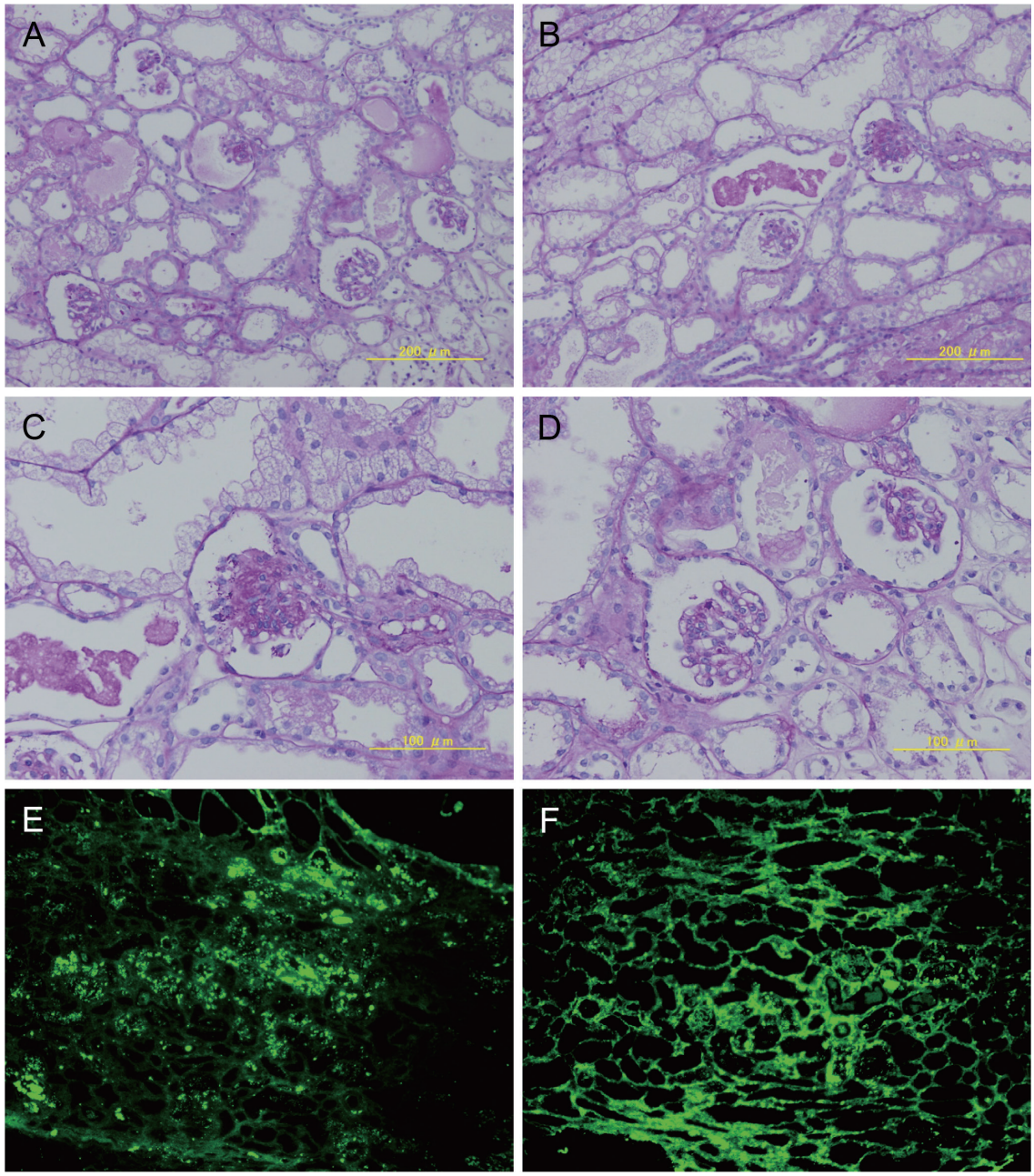

Fig. 3. Renal biopsy findings.
Light microscopy (periodic acid-Schiff staining) showed an edematous tubulointerstitial area with diffuse expanded tubules and immature glomeruli with sclerotic lesions (A-D). Immunofluorescence microscopy showed diffuse deposition of C3 (E) and fibrinogen (F) in the interstitial area. Original magnifications: A, B, E, F × 100; C, D × 200.

Complement dysregulation was suspected from repeated TMA findings, and genetic testing revealed heterozygous *CFI* mutations and *CFHR3-CFHR1* deficiency (Fig. 6).

First, we consider the relationship between spTMA and complement gene mutations. Several studies have reported that spTMA cases are associated with abnormal complement activation with decreased complement C3 and C4 levels, as seen in our case (Szilágyi et al. 2013; Bitzan et al. 2018). The pathophysiology of spTMA has not been fully elucidated. It is supposed that neuraminidase produced by *Streptococcus pneumoniae* exposes the normally masked Thomsen-Friedenreich (T) antigen present on the cell surface, and IgM antibodies against the T antigen produced in plasma cause hemolysis and vascular endothelial damage (Copelovitch and Kaplan 2008). Since CFH, an inhibitor of the alternative complement pathway, binds to sialic acid on the host cell surface, desialylation by neuraminidase impairs the binding of CFH to the cell surface, which may lead to abnormal complement activation (Ault 2000). Regarding complement gene abnormalities, Szilágyi et al. (2013) reported that three of five spTMA cases had gene mutations: previously published *CFI* mutation and two

Table 1. Atypical hemolytic uremic syndrome (aHUS) and nephrotic syndrome associated genes analyzed by target exome sequencing.

Gene symbol	Description
aHUS	
C3	Complement C3
CFB	Complement Factor B
CFH	Complement Factor H
CFI	Complement Factor I
PLG	Plasminogen
THBD	Thrombomodulin
CD46/MCP	CD46 Molecule
DGKE	Diacylglycerol Kinase Epsilon
Nephrotic syndrome	
ACTN4	Actinin Alpha 4
ANKFY1	Ankyrin Repeat And FYVE Domain Containing 1
ANLN	Anillin Actin Binding Protein
ARHGAP24	Rho GTPase Activating Protein 24
ARHGDIA	Rho GDP Dissociation Inhibitor Alpha
AVIL	Advillin
COL4A3	Collagen Type IV Alpha 3 Chain
COL4A4	Collagen Type IV Alpha 4 Chain
COL4A5	Collagen Type IV Alpha 5 Chain
COQ2	Coenzyme Q2, Polyprenyltransferase
COQ6	Coenzyme Q6, Monooxygenase
COQ8B/ADCK4	Coenzyme Q8B
CRB2	Crumbs Cell Polarity Complex Component 2
CUBN	Cubilin
EMP2	Epithelial Membrane Protein 2
EYA1	EYA Transcriptional Coactivator And Phosphatase 1
FAT1	FAT Atypical Cadherin 1
FN1	Fibronectin 1
GAPVD1	GTPase Activating Protein And VPS9 Domains 1
GON7	GON7 Subunit Of KEOPS Complex
INF2	Inverted Formin, FH2 And WH2 Domain Containing
ITGA3	Integrin Subunit Alpha 3
ITGB4	Integrin Subunit Beta 4
KANK1	KN Motif And Ankyrin Repeat Domains 1
KANK2	KN Motif And Ankyrin Repeat Domains 2
KANK4	KN Motif And Ankyrin Repeat Domains 4
LAGE3	L Antigen Family Member 3
LAMA5	Laminin Subunit Alpha 5
LAMB2	Laminin Subunit Beta 2
LMNA	Lamin A/C
LMX1B	LIM Homeobox Transcription Factor 1 Beta
MAGI2	Membrane Associated Guanylate Kinase, WW And PDZ Domain Containing 2
MT-TL1	Mitochondrially Encoded TRNA-Leu (UUA/G) 1
MYH9	Myosin Heavy Chain 9
MYO1E	Myosin IE
NPHS1	NPHS1 Adhesion Molecule, Nephrin
NPHS2	NPHS2 Stomatin Family Member, Podocin
NUP107	Nucleoporin 107

NUP133	Nucleoporin 133
NUP205	Nucleoporin 205
NUP93	Nucleoporin 93
OSGEP	O-Sialoglycoprotein Endopeptidase
PAX2	Paired Box 2
PDSS2	Decaprenyl Diphosphate Synthase Subunit 2
PLCE1	Phospholipase C Epsilon 1
PTPRO	Protein Tyrosine Phosphatase Receptor Type O
SCARB2	Scavenger Receptor Class B Member 2
SGPL1	Sphingosine-1-Phosphate Lyase 1
SMARCAL1	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A Like 1
TP53RK	TP53 Regulating Kinase
TPRKB	TP53RK Binding Protein
TRPC6	Transient Receptor Potential Cation Channel Subfamily C Member 6
TTC21B	Tetratricopeptide Repeat Domain 21B
WDR4	WD Repeat Domain 4
WDR73	WD Repeat Domain 73
WT1	WT1 Transcription Factor
XPO5	Exportin 5

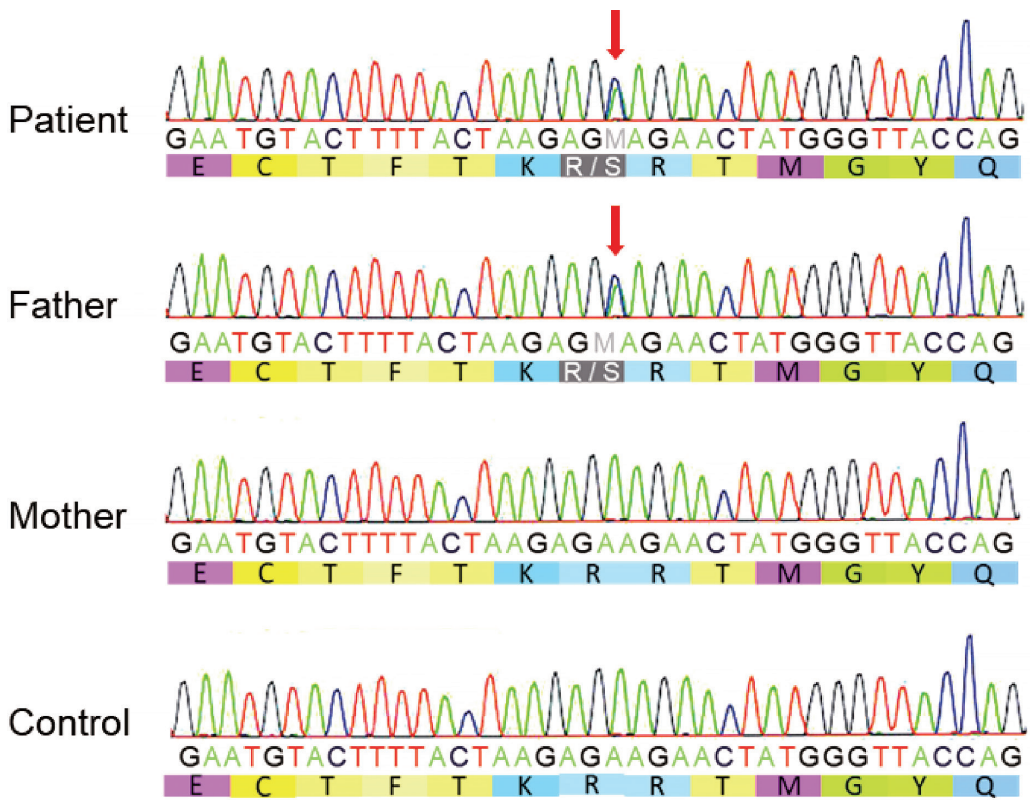

Fig. 4. Heterozygous mutation in the *CFI* gene.
Sanger sequencing confirmed a c.603A>C (p.Arg201Ser) mutation in exon 4 (chr4: 110,682,728) in the patient and his father.

novel mutations in the *CFH* and *TBHD*.

The pathogenicity of the *CFI* mutations and *CFHR* deletion identified in this patient should be considered in more detail. CFI is an inhibitor of complement activity that degrades activated complement proteins C3b and C4b in the presence of cofactors such as CFH (Nilsson et al. 2011).

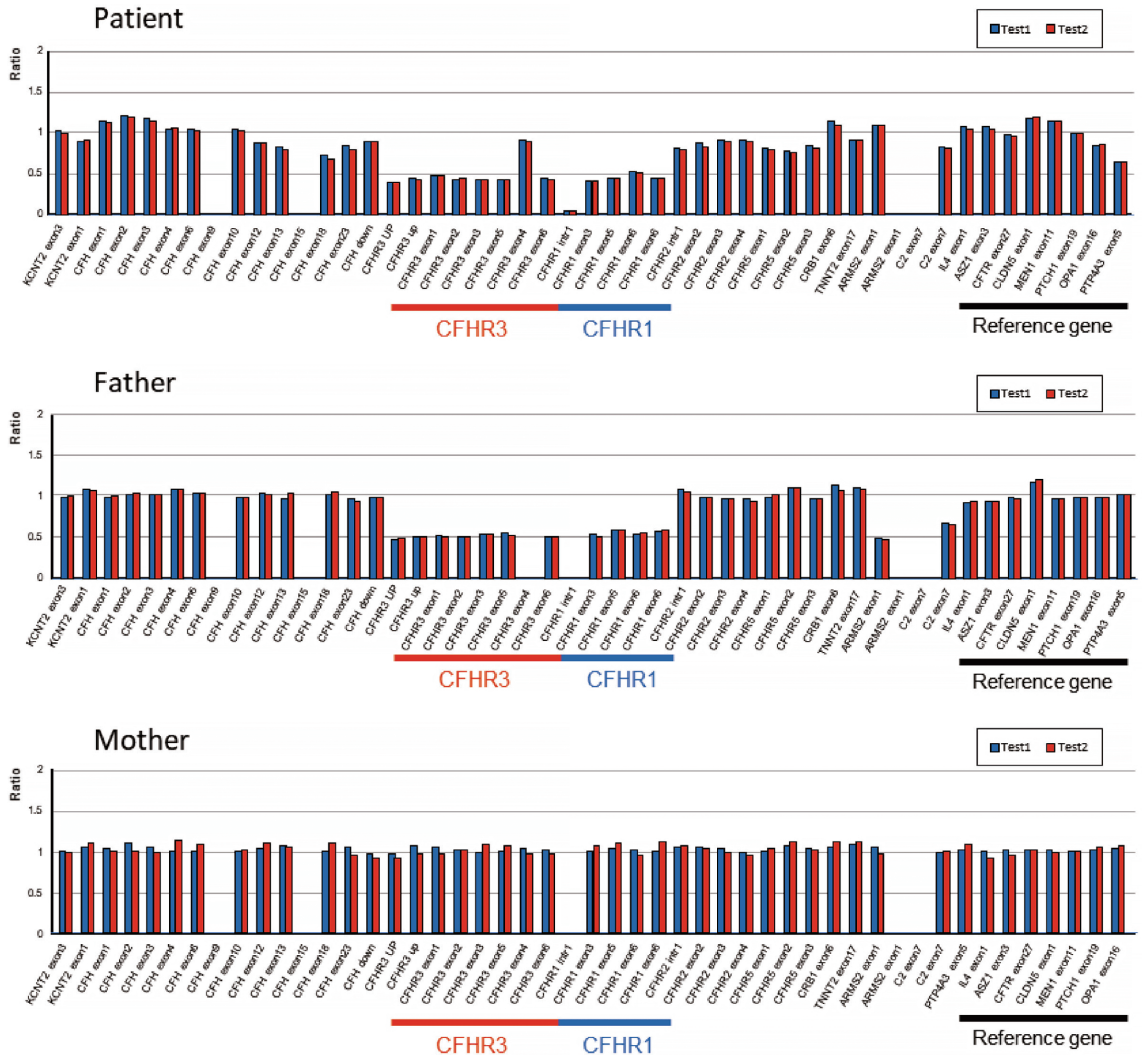

Fig. 5. Heterozygous deletions in *CFHR3* and *CFHR1* genes.
The multiplex ligation-dependent probe amplification (MLPA) method confirmed heterozygous deletions of *CFHR3* and *CFHR1* genes in the patient and his father.

CFI mutations are associated with aHUS and account for 4%-10% of aHUS cases in Europe and the United States (Noris and Remuzzi 2009), and most of the cases developed disease with heterozygous mutation of *CFI* (Bienaime et al. 2010; Nilsson et al. 2011). In contrast, there are currently no reported cases of *CFI* mutations with aHUS in Japan (Yoshida et al. 2019). It should also be noted that the mutation identified in our patient, *CFI* c.603A>C (p.R201S), is found in 3% of all Japanese individuals including healthy individuals (Yuasa et al. 2008).

Complement factor H-related (CFHR) gene alterations are also associated with aHUS, including the homozygous *CFHR3-CFHR1* deletion associated with anti-CFH antibody-positive aHUS (Józsi et al. 2008; Skerka et al. 2013); however, our case was a heterozygote of the deletion and was negative for anti-CFH antibody. *CFHR3-CFHR1* gene deletion is also found in healthy individuals, including in our patient's father who was asymptomatic. The allele frequency in Japanese individuals has been reported to be 0%-6.7% (Sivakumaran et al. 2011; Holmes et al. 2013), and it is considered to be a benign variant of a heterozygous deletion. However, Jodele et al. (2013) reported that heterozygous *CFHR3-CFHR1* deletion was identified in five of six patients with hematopoietic stem cell transplantation-associated TMA. In addition, Bello-Marquez et al. (2021) reported a case of aHUS complicated with NS, in which heterozygous *CFI* mutation and *CFHR* deletion were identified. This report supports the possibility that heterozygous *CFI* mutation and *CFHR3-CFHR1* deletion seen in our case may have been jointly involved in the development of TMA.

Since heavy proteinuria was observed in this case, the relationship between renal disease and TMA needs to be discussed. Renal biopsy showed FSGS and no findings of MPGN or findings such as endothelial swelling, arteriole and capillary thickening, or thrombosis often seen in patients with TMA (Noris and Remuzzi 2009; Manenti et al. 2013). However, if this case showed only NS, thrombo-

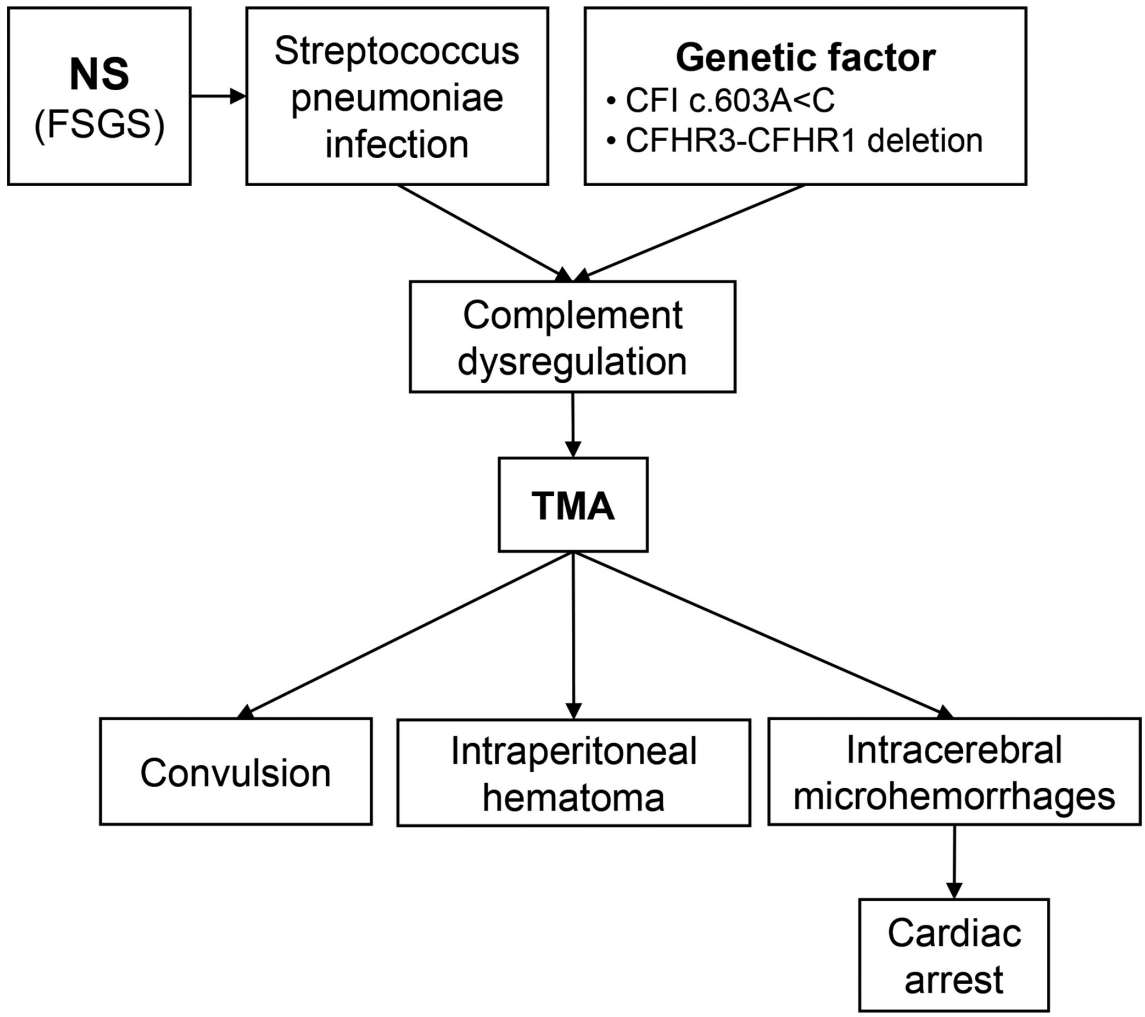

Fig. 6. Schema of the pathophysiology of this case.
NS, nephrotic syndrome; FSGS, focal segmental glomerulosclerosis.

cytopenia without DIC, schistocytes, convulsions and basal ganglia lesion without hypertension, and hypocomplementemia could not be explained, and these findings were clinically considered as TMA. In addition, we consider that the intra-abdominal hematoma and cardiac arrest are associated with TMA rather than NS-induced hypercoagulation since the contrast-enhanced CT at these times did not show any thrombosis. Cases of secondary TMA due to NS have rarely been reported (Manenti et al. 2013; Miyamoto et al. 2013; Nishi et al. 2020). Most of these NS-related TMA cases were refractory NS, especially FSGS, as in our case. However, cases of refractory NS appear to be rarely associated with TMA even under similar conditions, suggesting that host genetic factors may be the major factor in the development of TMA. In addition, NS is known as a risk factor of invasive pneumococcal disease, but there is only one case report of an NS patient with spTMA (Groves et al. 2016). In our case as well, NS is unlikely to be the direct cause of TMA.

Further, the adequacy of using eculizumab in this case warrants discussion. The use of eculizumab for aHUS has been established (Legendre et al. 2013), and it is recommended to exclude secondary TMA before using eculizumab (Kato et al. 2016). However, it has been reported to be effective in some patients with secondary TMA, including spTMA (Gilbert et al. 2013; Jeantet et al. 2019). If aHUS, a disease with a poor prognosis, is suspected, it is recommended to use eculizumab immediately (Loirat et al. 2016). In our case, renal function, thrombocytopenia, and complement C3 level improved after the initiation of eculizumab, suggesting dysregulation of complement activation. It is likely that our patient suffered from cardiac arrest due to cerebral hemorrhage or thrombosis in the presence of abnormal complement activation, and he may have survived if treatment had been started before the onset of coagulopathy.

This case report has some limitations that should be noted regarding the central nervous system symptoms. MRI findings associated with TMA are bilateral basal ganglia, brain stem, and deep white matter lesions on diffusion-weighted imaging (Hofer et al. 2014), and the basal ganglia lesions in our case are consistent with TMA lesions.

However, as the patient's convulsion preceded the appearance of thrombocytopenia and schistocytes, it was not possible to ascertain whether the initial convulsion and basal ganglia lesions were due to TMA. In addition, some congenital cases of NS such as Galloway-Mowat syndrome are complicated by neurological symptoms (Galloway and Mowat 1968; Vodopiutz et al. 2015; Braun et al. 2018). Although we did not identify any known NS-related gene mutations in this patient, we cannot rule out the possibility that the patient's neurological symptoms were due to congenital NS.

In conclusion, the heterozygous *CFI* mutation and *CFHR3-CFHR1* deletion in this patient may predispose to TMA under the strong trigger of pneumococcal infection. Further studies are needed to elucidate the pathophysiology of spTMA and the pathogenicity of these gene variants.

Conflict of Interest

The authors declare no conflict of interest.

References

Ault, B.H. (2000) Factor H and the pathogenesis of renal diseases. *Pediatr. Nephrol.*, **14**, 1045-1053.

Bello-Marquez, D.C., Nieto-Rios, J.F., Serna-Higuita, L.M. & Gonzalez-Vergara, A.J. (2021) Nephrotic syndrome associated with primary atypical hemolytic uremic syndrome. *J. Bras. Nefrol.*, **43**, 440-444.

Bienaime, F., Dragon-Durey, M.A., Regnier, C.H., Nilsson, S.C., Kwan, W.H., Blouin, J., Jablonski, M., Renault, N., Rameix-Welti, M.A., Loirat, C., Sautes-Fridman, C., Villoutreix, B.O., Blom, A.M. & Fremeaux-Bacchi, V. (2010) Mutations in components of complement influence the outcome of Factor I-associated atypical hemolytic uremic syndrome. *Kidney Int.*, **77**, 339-349.

Bitzan, M., AlKandari, O., Whittemore, B. & Yin, X.L. (2018) Complement depletion and Coombs positivity in pneumococcal hemolytic uremic syndrome (pnHUS). Case series and plea to revisit an old pathogenetic concept. *Int. J. Med. Microbiol.*, **308**, 1096-1104.

Braun, D.A., Shril, S., Sinha, A., Schneider, R., Tan, W., Ashraf, S., Hermle, T., Jobst-Schwan, T., Widmeier, E., Majmundar, A.J., Daga, A., Warejko, J.K., Nakayama, M., Schapiro, D., Chen, J., et al. (2018) Mutations in WDR4 as a new cause of Galloway-Mowat syndrome. *Am. J. Med. Genet. A*, **176**, 2460-2465.

Brocklebank, V., Wood, K.M. & Kavanagh, D. (2018) Thrombotic microangiopathy and the kidney. *Clin. J. Am. Soc. Nephrol.*, **13**, 300-317.

Copelovitch, L. & Kaplan, B.S. (2008) Streptococcus pneumoniae-associated hemolytic uremic syndrome. *Pediatr. Nephrol.*, **23**, 1951-1956.

Galloway, W.H. & Mowat, A.P. (1968) Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. *J. Med. Genet.*, **5**, 319-321.

Gilbert, R.D., Nagra, A. & Haq, M.R. (2013) Does dysregulated complement activation contribute to haemolytic uraemic syndrome secondary to Streptococcus pneumoniae? *Med. Hypotheses*, **81**, 400-403.

Groves, A.P., Reich, P., Sigdel, B. & Davis, T.K. (2016) Pneumococcal hemolytic uremic syndrome and steroid resistant nephrotic syndrome. *Clin. Kidney J.*, **9**, 572-575.

Hinkes, B.G., Mucha, B., Vlangos, C.N., Gbadegesin, R., Liu, J., Hasselbacher, K., Hangan, D., Ozaltin, F., Zenker, M. & Hildebrandt, F.; Arbeitsgemeinschaft fur Paediatrische Nephrologie Study Group (2007) Nephrotic syndrome in the first year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). *Pediatrics*, **119**, e907-919.

Hofer, J., Rosales, A., Fischer, C. & Giner, T. (2014) Extra-renal manifestations of complement-mediated thrombotic microangiopathies. *Front. Pediatr.*, **2**, 97.

Holmes, L.V., Strain, L., Staniforth, S.J., Moore, I., Marchbank, K., Kavanagh, D., Goodship, J.A., Cordell, H.J. & Goodship, T.H. (2013) Determining the population frequency of the CFHR3/CFHR1 deletion at 1q32. *PLoS One*, **8**, e60352.

Jeantet, G., Pernin, V., Brunot, V., Roccabianca, A., Macombe, A., Szwarc, I., Klouche, K., Loirat, C., Mourad, G., Fremeaux-Bacchi, V. & Le Quintrec, M. (2019) Successful treatment of a *Streptococcus pneumoniae*-associated haemolytic uraemic syndrome by eculizumab. *Clin. Kidney J.*, **12**, 106-109.

Jodele, S., Licht, C., Goebel, J., Dixon, B.P., Zhang, K., Sivakumaran, T.A., Davies, S.M., Pluthero, F.G., Lu, L. & Laskin, B.L. (2013) Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. *Blood*, **122**, 2003-2007.

Jokiranta, T.S. (2017) HUS and atypical HUS. *Blood*, **129**, 2847-2856.

Józsi, M., Licht, C., Strobel, S., Zipfel, S.L., Richter, H., Heinen, S., Zipfel, P.F. & Skerka, C. (2008) Factor H autoantibodies in atypical hemolytic uremic syndrome correlate with CFHR1/CFHR3 deficiency. *Blood*, **111**, 1512-1514.

Kato, H., Nangaku, M., Hataya, H., Sawai, T., Ashida, A., Fujimaru, R., Hidaka, Y., Kaname, S., Maruyama, S., Yasuda, T., Yoshida, Y., Ito, S., Hattori, M., Miyakawa, Y., Fujimura, Y., et al. (2016) Clinical guides for atypical hemolytic uremic syndrome in Japan. *Clin. Exp. Nephrol.*, **20**, 536-543.

Legendre, C.M., Licht, C., Muus, P., Greenbaum, L.A., Babu, S., Bedrosian, C., Bingham, C., Cohen, D.J., Delmas, Y., Douglas, K., Eitner, F., Feldkamp, T., Fouque, D., Furman, R.R., Gaber, O., et al. (2013) Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N. Engl. J. Med.*, **368**, 2169-2181.

Loirat, C., Fakhouri, F., Ariceta, G., Besbas, N., Bitzan, M., Bjerre, A., Coppo, R., Emma, F., Johnson, S., Karpman, D., Landau, D., Langman, C.B., Lapeyraque, A.L., Licht, C., Nester, C., et al. (2016) An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr. Nephrol.*, **31**, 15-39.

Malaker, R., Saha, S., Hanif, M., Ahmed, A., Saha, S., Hasanuzzaman, M., Khondakar, T., Islam, M., Baqui, A.H., Santosham, M., Darmstadt, G.L., Whitney, C.G. & Saha, S.K. (2019) Invasive pneumococcal infections in children with nephrotic syndrome in Bangladesh. *Pediatr. Infect. Dis. J.*, **38**, 798-803.

Manenti, L., Gnappi, E., Vaglio, A., Allegri, L., Noris, M., Bresin, E., Pilato, F.P., Valoti, E., Pasquali, S. & Buzio, C. (2013) Atypical haemolytic uraemic syndrome with underlying glomerulopathies. A case series and a review of the literature. *Nephrol. Dial. Transplant.*, **28**, 2246-2259.

Miyamoto, T., Ishikawa, Y., Yamamoto, J., Yamamura, T. & Kawata, T. (2013) Thrombotic microangiopathy secondary to steroid pulse therapy administered for refractory nephrotic syndrome. *Intern. Med.*, **52**, 2099-2103.

Nilsson, S.C., Sim, R.B., Lea, S.M., Fremeaux-Bacchi, V. & Blom, A.M. (2011) Complement factor I in health and disease. *Mol. Immunol.*, **48**, 1611-1620.

Nishi, K., Sato, M., Ogura, M., Okutsu, M., Ishikura, K. & Kamei, K. (2020) Two cases of idiopathic steroid-resistant nephrotic syndrome complicated with thrombotic microangiopathy. *BMC Nephrol.*, **21**, 323.

Noris, M. & Remuzzi, G. (2009) Atypical hemolytic-uremic syndrome. *N. Engl. J. Med.*, **361**, 1676-1687.

Scobell, R.R., Kaplan, B.S. & Copelovitch, L. (2020) New

insights into the pathogenesis of Streptococcus pneumoniae-associated hemolytic uremic syndrome. *Pediatr. Nephrol.*, **35**, 1585-1591.

Sivakumaran, T.A., Igo, R.P. Jr., Kidd, J.M., Itsara, A., Kopplin, L.J., Chen, W., Hagstrom, S.A., Peachey, N.S., Francis, P.J., Klein, M.L., Chew, E.Y., Ramprasad, V.L., Tay, W.T., Mitchell, P., Seielstad, M., et al. (2011) A 32 kb critical region excluding Y402H in CFH mediates risk for age-related macular degeneration. *PLoS One*, **6**, e25598.

Skerka, C., Chen, Q., Fremeaux-Bacchi, V. & Roumenina, L.T. (2013) Complement factor H related proteins (CFHRs). *Mol. Immunol.*, **56**, 170-180.

Szilágyi, Á., Kiss, N., Bereczki, C., Talosi, G., Racz, K., Turi, S., Gyorke, Z., Simon, E., Horvath, E., Kelen, K., Reusz, G.S., Szabo, A.J., Tulassay, T. & Prohaszka, Z. (2013) The role of complement in Streptococcus pneumoniae-associated haemolytic uraemic syndrome. *Nephrol. Dial. Transplant.*, **28**, 2237-2245.

Vodopiutz, J., Seidl, R., Prayer, D., Khan, M.I., Mayr, J.A., Streubel, B., Steiss, J.O., Hahn, A., Csaicsich, D., Castro, C., Assoum, M., Muller, T., Wieczorek, D., Mancini, G.M., Sadowski, C.E., et al. (2015) WDR73 mutations cause infantile neurodegeneration and variable glomerular kidney disease. *Hum. Mutat.*, **36**, 1021-1028.

Yoshida, Y., Kato, H., Ikeda, Y. & Nangaku, M. (2019) Pathogenesis of atypical hemolytic uremic syndrome. *J. Atheroscler. Thromb.*, **26**, 99-110.

Yuasa, I., Nakagawa, M., Umetsu, K., Harihara, S., Matsusue, A., Nishimukai, H., Fukumori, Y., Saitou, N., Park, K.S., Jin, F., Lucotte, G., Chattopadhyay, P.K., Henke, L. & Henke, J. (2008) Molecular basis of complement factor I (CFI) polymorphism: one of two polymorphic suballeles responsible for CFI A is Japanese-specific. *J. Hum. Genet.*, **53**, 1016-1021.