Table 3 Subgroup analysis of the percentage of patients who had achieved the platelet count $\geq 50 \times 10^9$/L at week 24 after administration of the study drug

Subgroups	*n*	No. of patients who achieved	%	Two-sided 95 % CI of the percentage
Duration of ITP (median: 5.9 years) (years)				
<5.9	13	6	46.2	(19.2, 74.9)
≥5.9	13	2	15.4	(1.9, 45.4)
Had splenectomy				
No	22	6	27.3	(10.7, 50.2)
Yes	4	2	50.0	(6.8, 93.2)
Had concomitant drugs for ITP at baseline				
None	5	3	60.0	(14.7, 94.7)
Yes	21	5	23.8	(8.2, 47.2)
Baseline platelet count (/L)				
$<15 \times 10^9$	6	2	33.3	(4.3, 77.7)
$\geq 15 \times 10^9$	20	6	30.0	(11.9, 54.3)
Previously received thrombopoietin receptor agonists				
No	19	7	36.8	(16.3, 61.6)
Yes	7	1	14.3	(0.4, 57.9)
Number of previous therapies for ITP				
<3	17	7	41.2	(18.4, 67.1)
≥3	9	1	11.1	(0.3, 48.2)

levels were not significantly changed from the baseline over 24-week study period.

Safety

Three serious adverse events required inpatient hospitalization were reported in three patients: one patient with grade 3 viral infection, one with grade 2 viral infection and one with grade 2 hypermenorrhea. All these three events recovered by supportive treatment and the patients discharged from the hospital in a week. The causal relationship of all the serious adverse events with rituximab was not completely ruled out.

The other adverse drug reactions (ADRs) that occurred in two or more patients were upper respiratory tract infection and headache in three patients each, and diarrhea, abdominal pain, malaise, and cough in two patients each. All these ADRs were grade 1 or 2 in severity.

Infusion related reactions were observed in eight patients and those that occured in two or more patients were fever, oropharyngeal pain, headache, pruritus, urticaria, and hypersensitivity, all of which were grade 1 or 2 in severity. Infusion related reactions were most frequently observed at the initial administration of rituximab (at week 0) among the injection-time points in the 4-dose study drug regimen. None of patients had adverse events led to discontinuation of the study drug, and no deaths were reported in this study.

Discussion

The response rate of the primary efficacy endpoint in this study, the percentage of patients with the platelet count $\geq 50 \times 10^9$/L at week 24 after the first administration of rituximab, was 30.8 % (95 % CI 14.3–51.8 %), and failed to meet the pre-determined statistical criteria of the lower confidence limit of 20 %.

However, the efficacy of rituximab in patients with chronic refractory ITP in this study is substantial when compared with the modest response rate of 2 % (1/42 patients; 95 % CI 0, 12.6 %) in placebo group reported in other clinical studies in patients with refractory ITP [13]. Also, as seen in the subgroup analysis, even heavily treated patients with chronic refractory ITP in this study exhibited moderate efficacy, with the platelet count $\geq 50 \times 10^9$/L at week 24, to rituximab as shown below: 50.0 % (2/4 patients) of patients who underwent splenectomy and 14.3 % (1/7 patients) of patients who previously received thrombopoietin receptor agonists. This trend becomes much clearer in this study when considering clinical benefit to patients who are at risk of fatal bleeding (i.e., the platelet count $\leq 30 \times 10^9$/L). As additional analysis, the percentages of patients with the platelet count $\geq 30 \times 10^9$/L at week 24 after administration of the study drug were evaluated, and rituximab then showed considerably high effectiveness in a total of patients (57.7 %, 15/26 patients) as well as patients previously heavily treated, who underwent splenectomy (75.0 %, 3/4 patients) and who received

thrombopoietin receptor agonists (71.4 %, 5/7 patients). These lines of evidence suggest that rituximab can clinically useful for the treatment of Japanese patients with chronic refractory ITP.

The goal of treatment in ITP is to maintain the platelet count which reduces the risk of bleeding while minimizing treatment-related toxicity. To accomplish this goal, thrombopoietin receptor agonists are recently used. However, thrombocytopenia usually recurring shortly after the drug withdrawal is known as one of the drawbacks of these agonists. Thus, these agents are indefinitely used to maintain the platelet count to minimize bleeding [16]. In the sense, this study showed that rituximab's effect lasted longer after completion of treatment; the platelet counts at all the time points exceeded 30 $\times$ 10^9/L until week 24 after the last dose of the study drug at week 3.

Clinical significance of rituximab in patients with ITP is still being investigated extensively outside Japan to position the therapy at an alternative treatment for ITP prior to splenectomy [15–18]. Although the details of study design was varied from study to study in terms of target population (e.g., newly diagnosed or relapsed ITP), concomitant therapy (e.g., with or without steroids), dosage and administration of rituximab (e.g., 4-weekly 375 mg/m^2 or 2-times 1000 mg 2 weeks apart), and endpoints of efficacy analysis, rituximab commonly showed a clinically substantial efficacy and well tolerability in patients with ITP. Especially, several studies showed a clinically meaningful sustained response to have a chance for sparing splenectomy [12, 18–23], supporting our results in this study. Regarding the safety of rituximab, we observed severe adverse events in three patients. Two had viral infection of unknown etiology and one had hypermenorrhea. All three events were resolved by supportive treatment and all patients were discharged from hospital within a week of admission.

We, thus, conclude from the above-mentioned results that rituximab is clinically useful and involves no particular safety concerns in the treatment of Japanese patients with chronic refractory ITP.

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Compliance with ethical standards

Conflict of interest Dr. Miyakawa reports non-financial support from Zenyaku Kogyo, grants from Japan Medical Association Center for Clinical Trials (JMACCT), during the conduct of the study; grants and personal fees from Alexion pharmaceutical, personal fees from Daiichi Sankyo, personal fees from Fuji film, personal fees from GlaxoSmithKline, personal fees from Kyowa-Hakko Kirin, personal fees from Ono pharmaceuticals, outside the submitted work; Dr. Kanakura reports grants from Chugai Pharmaceutical Co. Ltd., personal fees from Zenyaku-Kogyo, during the conduct of the study; grants and personal fees from Kyowa-Hakkyo Kirin Co. Ltd., grants and personal fees from Otsuka Pharmaceutical Co. Ltd., grants from Takeda Pharmaceutical Co. Ltd., grants from Teijin Pharma, grants from Janssen Pharmaceutical Co. Ltd., grants and personal fees from Alexion Pharmaceutical Co. Ltd., personal fees from Shire Co. Ltd., grants from Bristol-Myers Squibb Co. Ltd., outside the submitted work; Dr. Yano has nothing to disclose. Dr. Shirasugi reports personal fees from Kyowa-Hakko Kirin, personal fees from Pfizer, personal fees from Ono pharmaceutical, personal fees from Bristol-Myers Squibb, personal fees from Celgene, personal fees from GlaxoSmithKline, outside the submitted work; Dr. Higashihara reports grants and personal fees from Chugai pharmaceutical, during the conduct of the study; grants and personal fees from Kyowa-Hakko Kirin, grants from MSD, grants from Jannsen pharmaceutical, grants from Takeda, personal fees from Sumitomo Dainippon pharma, grants from Teijin, grants from Astellas pharma, personal fees from GlaxoSmithKline, outside the submitted work; Dr. Nishiwaki reports grants from Zenyaku Kogyo Company, Limited, grants from Chugai Pharmaceutical, grants from Novartis Pharma K.K., outside the submitted work; Dr. Okamoto reports grants from Chugai pharmaceuticals, during the conduct of the study; personal fees from KyowaHakkoKirin, personal fees from Takeda, personal fees from Bristol-Myers Squibb, personal fees from Janssen pharmaceutical, personal fees from Celgene, personal fees from Alexion, personal fees from Eisai, grants from GlaxoSmithKline, outside the submitted work; Dr. Katsutani has nothing to disclose. Dr. Nomura has nothing to disclose. Dr. Kikuchi has nothing to disclose. Dr. Abe has nothing to disclose. Dr. Nishikawa has nothing to disclose. Dr. Ozaki reports grants from Japan Medical Association Center for Clinical Trials, during the conduct of the study; personal fees from Nippon Shinyaku, personal fees from Janssen pharmaceutical companies, personal fees from Chugai pharmaceutical, personal fees from Celgene, personal fees from Kyowa-Hakko Kirin pharmaceutical, outside the submitted work; Dr. Ikeda reports personal fees from Chugai pharmaceuticals, during the conduct of the study; personal fees from Novartis, personal fees from Sanofi, personal fees from Daichi Sankyo, outside the submitted work; Dr. Tomiyama reports grants from JMACCT, during the conduct of the study; personal fees from GSK, personal fees from Novartis, personal fees from Kyowa-Hokko Kirin, personal fees from Eisai, personal fees from Sysmex, outside the submitted work; Dr. Fujimura reports non-financial support from Kyowa-Hakko Kirin, during the conduct of the study; non-financial support from Medical support, outside the submitted work.

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ORIGINAL ARTICLE

Genetic variations in complement factors in patients with congenital thrombotic thrombocytopenic purpura with renal insufficiency

Xinping Fan[1,6] · Johanna A. Kremer Hovinga[2] · Hiroko Shirotani-Ikejima[1] · Yuka Eura[1] · Hidenori Hirai[1] · Shigenori Honda[1] · Koichi Kokame[1] · Magnus Mansouri Taleghani[2] · Anne-Sophie von Krogh[3,4] · Yoko Yoshida[5] · Yoshihiro Fujimura[5] · Bernhard Lämmle[2,7] · Toshiyuki Miyata[1,8]

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Abstract The congenital form of thrombotic thrombocytopenic purpura (TTP) is caused by genetic mutations in ADAMTS13. Some, but not all, congenital TTP patients manifest renal insufficiency in addition to microangiopathic hemolysis and thrombocytopenia. We included 32 congenital TTP patients in the present study, which was designed to assess whether congenital TTP patients with renal insufficiency have predisposing mutations in complement regulatory genes, as found in many patients with atypical hemolytic uremic syndrome (aHUS). In 13 patients with severe renal insufficiency, six candidate complement or complement regulatory genes were sequenced and 11 missense mutations were identified. One of these missense mutations, C3:p.K155Q mutation, is a rare mutation located in the macroglobulin-like 2 domain of C3, where other mutations predisposing for aHUS cluster. Several of the common missense mutations identified in our study have been reported to increase disease-risk for aHUS, but were not more common in patients with as compared to those without renal insufficiency. Taken together, our results show that the majority of the congenital TTP patients with renal insufficiency studied do not carry rare genetic mutations in complement or complement regulatory genes.

Keywords Atypical hemolytic uremic syndrome · Complement factors · Renal insufficiency · Thrombotic thrombocytopenic purpura · Upshaw–Schulman syndrome

✉ Johanna A. Kremer Hovinga
johanna.kremer@insel.ch

✉ Toshiyuki Miyata
miyata@ncvc.go.jp

1 Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center, Suita, Japan

2 Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital and University of Bern, 3010 Bern, Switzerland

3 Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

4 Department of Hematology, St Olavs Hospital Trondheim University Hospital, Trondheim, Norway

5 Department of Blood Transfusion Medicine, Nara Medical University, Kashihara, Japan

6 Department of Clinical Laboratory, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

7 Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Mainz, Germany

8 Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

Introduction

Thrombotic thrombocytopenic purpura (TTP), one form of thrombotic microangiopathy, is characterized by microangiopathic hemolytic anemia and thrombocytopenia. The congenital form of TTP, also known as Upshaw–Schulman syndrome, is caused by a severe constitutional deficiency of ADAMTS13 due to homozygous or compound heterozygous *ADAMTS13* mutations [1, 2] and is assumed to represent less than 5 % of all TTP cases. The age at disease onset is variable. Some congenital TTP patients present with overt TTP soon after birth, others experience first signs only in adulthood, e.g., triggered by pregnancy, or even remain asymptomatic into their fifth or sixth decades of life [3, 4]. Clinical manifestations in congenital TTP are also heterogeneous. Besides the classical hematological

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findings, some patients show neurological symptoms, others kidney involvement up to renal failure. Both onset during pregnancy and kidney involvement are noteworthy as they are features also observed in atypical hemolytic uremic syndrome (aHUS), another type of thrombotic microangiopathy [5, 6]. Approximately 60 % of aHUS cases can be explained by dysregulation and/or excessive activation of the alternative pathway of the complement system due to mutations in complement regulatory genes (*CFH*, *MCP*, *CFI*, *THBD*), hyperfunctional mutations of complement factors (*C3*, *CFB*) or autoantibodies against complement factor H [5, 6]. Recently, mutations in the diacylglycerol kinase epsilon gene were reported to co-segregate with phenotypic aHUS [7, 8].

To explain the variable clinical phenotypes in congenital TTP, genetic mutations responsible for increased activation of the complement system may influence the severity of renal involvement and thus serve as disease modifiers. Of note in this context is the study of Noris et al. who reported on two sisters with congenital TTP who showed different clinical phenotypes [9]. One sister manifested exclusively with neurologic symptoms while the other sister had very severe renal insufficiency that required chronic dialysis. In the latter, a missense mutation in complement factor H was identified which was not present in the sister with neurologic symptoms only. These data suggest that increased activation of the complement system due to genetic mutations modifies the severity of renal involvement in congenital TTP, a scenario derived from a single-family and to be verified in a larger number of patients.

In the present study, we explored whether genetic mutations in complement or complement regulatory genes leading to increased activation of the complement system contribute to the clinical phenotype of congenital TTP patients with predominant renal involvement.

Patients and methods

Patients

From two congenital TTP cohorts, that of the Hemostasis Research Laboratory in Bern, Switzerland [10, 11] and the Japanese congenital TTP study [4], confirmed congenital TTP patients were selected based on the following two criteria: (1) the patient had not been extensively studied by other groups and (2) whole blood for DNA extraction was available. A total of 32 congenital TTP patients (30 from Europe and 2 from Japan) were included in this study, of which thirteen had severe renal insufficiency up to end-stage renal disease (Table 1). The definition for renal involvement was as follows: (1) acute renal insufficiency during one or more acute TTP bouts requiring dialysis, or (2) chronic kidney disease defined according to KDIGO (kidney disease: improving global outcomes) as persistence of a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 or albuminuria for at least 3 months, with or without arterial hypertension; or (3) end-stage renal disease requiring renal replacement therapy (either dialysis or kidney transplant); or (4) documented tissue damage on renal biopsy; or (5) having a diagnosis of (atypical) hemolytic uremic syndrome established by a nephrologist based on the concomitant presence of thrombocytopenia, microangiopathic hemolytic anemia and renal insufficiency. All patients had severe ADAMTS13 deficiency (<10 % of the normal) in the absence of a functional inhibitor on at least two time points, at least two ADAMTS13 mutations and/or a plasma infusion trial demonstrating full recovery of infused ADAMTS13 and a plasma half-life of ADAMTS13 of 2–4 days. The plasma ADAMTS13 activity was measured as previously described [12–14]. The study was approved by the Institutional Review Board of each institution.

Genetic analysis

The coding exons and flanking intronic regions of *CFH, C3, MCP, CFI, CFB,* and *THBD* were sequenced as described previously [15, 16] in all 13 congenital TTP patients presenting with renal insufficiency. In the remaining 19 European congenital TTP patients without renal involvement, only a limited analysis of the 11 genetic missense mutations identified in the patients with renal insufficiency was performed. The allele frequencies of the found 11 missense mutations between the 11 European congenital TTP patients with renal involvement and the 19 European congenital TTP patients without renal involvement were compared by Chi square analysis. The nomenclature system of the amino acid and nucleotide numbers is given according to the recommendation of the Human Genome Variation Society. The A of the ATG of the initial Met codon is denoted as nucleotide +1, and the initial Met residue is denoted as amino acid +1. Multiplex ligation-dependent probe amplification analysis was used to screen for deletions of *CFH* and *CFHR*s using a commercially available kit (MLPA kit P236-A2; MRC-Holland, the Netherlands) [15]. The possible impact of the identified genetic mutations on structure and function of the respective proteins was examined by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html). The crystal structure of the complex of C3b and CCP 1-4 domains of CFH (ID: 2WII) [17] was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). Molecular graphic imaging and analysis were generated using the PyMOL molecular visualization system (Schrödinger, Portland, OR).

Table 1 Clinical characteristics and genetic variations of 13 congenital TTP patients with renal insufficiency

Patient ID	Current age (y)	Sex	CFH			C3			CFI
			rs800292	rs1061170	rs1065489	rs2230199	rs147859257	rs1047286	rs145769028
			c.184G > A	c.1204T > C[a]	c.2808G > T	c.304C > G	c.463A > C	c.941C > T	c.603A > C
1	36	F		p.Y402H		p.R102G	**p.K155Q**[b]	p.P314L	
2	53	M		p.Y402H	p.E936D				
3	61	M	p.V62I						
4	33	M	p.V62I (homo)						
5	61	F		p.Y402H	p.E936D				
6	38	M	p.V62I			p.R102G		p.P314L	
7	29	F	p.V62I (homo)			p.R102G		p.P314L	
8	48	F	p.V62I	p.Y402H					
9	44	F		p.Y402H (homo)		p.R102G		p.P314L	
10	46	M							
11	29	F		p.Y402H	p.E936D	p.R102G		p.P314L	
12	43	M			p.E936D (homo)				
13	35	M	p.V62I		p.E936D (homo)				**p.R201S**[c]
NHLBI GO Exome Sequencing Project									
MAF			39 %	38 %	14 %	15 %	0.3 %	15 %	None
1000 Genomes Project									
MAF, EUR			26 %	36 %	18 %	22 %	0 %	21 %	0 %
MAF, JPT			41 %	7 %	46 %	0 %	0 %	0 %	2 %

Table 1 continued

Patient ID	CFB			THBD	Number of CFHR1-R3 allele	ADAMTS13			Clinical characteristics
	rs4151667	rs641153	rs4151651	rs1042579		Amino acid and/or nucleotide change	Amino acid and/or nucleotide change	Activity (%)	
	c.26T > A	c.95G > A	c.754G > A	c.1418C > T					
1	**p.L9H**[c]			p.A473V	2	p.D235H	p.W542G	3.5[d]	Adult onset during 1st pregnancy with renal complications and renal sequelae
2			**p.G252S**[c]		2	c.4143_4144 insA p.E1382Rfs*6	c.4143_4144 insA p.E1382Rfs*6	<1[d]	Acute bouts always with severe renal insufficiency
3			**p.G252S**[c]	p.A473V	0	c.4143_4144 insA p.E1382Rfs*6	c.4143_4144 insA p.E1382Rfs*6	<1[d]	Acute bouts with severe renal insufficiency requring dialysis; triggered by (mild/moderate) alcohol consumption
4		p.R32Q (homo)		p.A473V	2	c.4143_4144 insA p.E1382Rfs*6	c.4143_4144 insA p.E1382Rfs*6	<1[d]	Original diagnosis recurrent HUS
5				p.A473V	2	p.R507Q	c.4143_4144 insA p.E1382Rfs*6	<1[d]	End-stage renal disease and kidney transplantation
6		p.R32Q			1	p.G1239 V	p.G1239 V	<1[d]	In adulthood acute bouts always with severe renal insufficiency requring dialysis; triggered always by alcohol consumption
7					2	p.R692C	c.3044 + 2430_ 3568 + 81del3291	<3[e]	End-stage renal disease
8		p.R32Q			2	c.2000delA p.N667Tfs*31	p.R1219Q	3[d]	Renal sequelae
9					2	p.Y177C	p.R1060W	1.5 in acute bout, 5 in remission[d]	Original diagnosis aHUS/membranoproliferative glomerulonephritis
10		p.R32Q		p.A473V	0	p.L232Q	p.R1060W	1 in acute bout, 5.3 in remission[d]	Renal sequelae
11					2	p.R1095Q	not identified	<1[d]	Renal sequelae

Table 1 continued

Patient ID	CFB			THBD	Number of CFHR1-R3 allele	ADAMTS13			Clinical characteristics
	rs4151667	rs641153	rs4151651	rs1042579		Amino acid and/or nucleotide change	Amino acid and/or nucleotide change	Activity (%)	
	c.26T > A	c.95G > A	c.754G > A	c.1418C > T					
12				p.A473V	2	p.H234Q	p.R1206*	<0.5[f]	Acute bouts with renal insufficiency
13				p.A473V	2	c.1885delA p.R629Efs*69	p.C908Y	<0.5[f]	Original diagnosis aHUS; acute bouts with severe renal insufficiency requring dialysis; triggered by heavy alcohol consumption
NHLBI GO Exome Sequencing Project									
MAF	3 %	12 %	3 %	14 %					All NHLBI participants, 13,006 alleles
1000 Genomes Project									
MAF, EUR	5 %	9 %	3 %	19 %					European (CEU, FIN, GBR, IBS, TSI), 1006 alleles
MAF, JPT	4 %	7 %	0 %	26 %					Japanese, 208 alleles

Patient ID 1–11 are from Swiss registry and patient ID 12 and 13 are from Japan registry. Nonsynonymous mutations were not identified in the MCP gene

The A of the ATG of the initial Met codon is denoted as nucleotide +1, and the initial Met residue is denoted as amino acid +1

The MAF of the NHLBI GO Exome Sequencing Project was obtained from http://evs.gs.washington.edu/EVS/, and the MAF of the 1000 Genomes Project Phase 3 was obtained from http://www.1000genomes.org/analysis

TTP thrombotic thrombocytopenic purpura, *aHUS* atypical hemolytic uremic syndrome, *MAF* minor allele frequency

[a] Reference sequence of CFH (NM 000186.3) is c.1204C > T

[b] Bold and underlined, rare and potentially predisposing mutation

[c] Bold, low frequency mutation

[d] The ADAMTS13 activity was measured by FRETS-VWF73 assay

[e] Quantitative immunoblotting assay, or

[f] Act-ELISA assay

In two European patients (Table 1, patient ID 7 and 11), only a single causative *ADAMTS13* mutation had been identified. Therefore, we employed the newly developed genomic quantitative PCR method [18] to identify a second causative mutation.

Results

To identify genetic mutations in complement genes leading to increased activation of the alternative pathway of the complement system, we performed DNA sequencing of the 6 candidate genes, *CFH*, *C3*, *MCP*, *CFI*, *CFB*, and *THBD* and identified 11 missense mutations in 13 congenital TTP patients with renal insufficiency (Table 1). We retrieved the allele frequency of these missense mutations from population cohorts participating in the NHLBI GO Exome Sequencing Project and the 1000 Genomes project Phase 3 and found that C3:p.K155Q is a rare mutation with a minor allele frequency (MAF) of 0.3 % and the two CFB missense mutations, p.L9H and p.G252S, are low frequency mutations with a MAF of 3 % (Table 1). These three missense mutations were observed in the European patients. One Japanese patient (ID 13) with renal insufficiency carried the one Japanese-specific CFI missense mutation, p.R201S, which is a low frequency mutation with a MAF of 2 % in the Japanese population [19]. The remaining 7 missense mutations were classified as common mutations with a MAF of more than 5 %.

We also genotyped the found 10 missense mutations, with exclusion of one Japanese-specific mutation, in the 19 European congenital TTP patients without renal involvement (data not shown). C3:p.K155Q was not identified in this group. None of the remaining 9 missense mutations found in the European congenital TTP patients was significantly more common among patients with compared to those without renal involvement.

Since the *ADAMTS13* mutation, 4143_4144 insA, is frequent among patients with congenital ADAMTS13 deficiency in Northern and Central European countries [20], it was frequent in our cohort of European origin. Three of 11 (27.3 %) European congenital TTP patients with renal involvement were homozygous carriers for the frequent *ADAMTS13* mutation 4143_4144insA, as were 6/19 (31.6 %) European congenital TTP patients without renal involvement. Though no difference in plasma ADAMTS13 activity between congenital TTP patients with and without renal involvement was observed, patients without renal involvement were younger (median 33 years, range 14–75 years) than patients with renal involvement (median 43 years, range 29–61 years).

We have recently developed a new genomic quantitative PCR method to identify large gene deletions in the *ADAMTS13* gene [18]. Employing this method, we identified a second causative mutation in patient ID 7 *ADAMTS13* c.3044 + 2430_3568 + 81del3291, a 3291-bp deletion including exons 24 and 25. In patient ID 11, no large deletion was observed and though the obligatory second mutation still remains unknown, the plasma infusion trial confirmed the congenital TTP diagnosis in this patient.

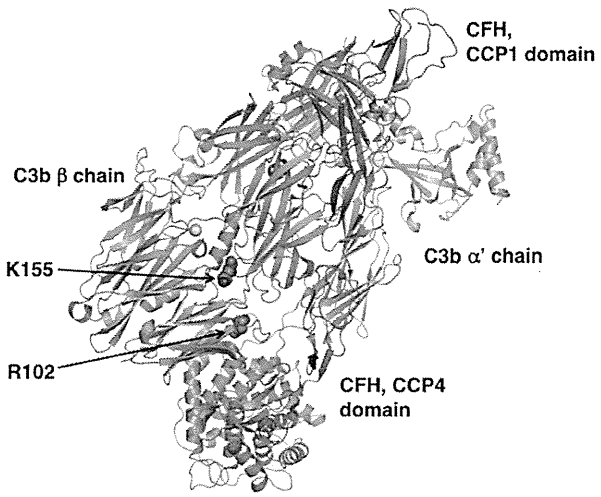

Fig. 1 Location of the C3:p.K155Q and C3:p.R102G mutations in the C3b-CFH CCP1-4 complex. C3b β-chain containing macroglobulin-like domains (MG) 1-5 is shown in *blue* and C3b α'-chain is shown in *green*. Complement control protein (CCP) domains 1-4 in CFH are depicted in *orange*. A calcium ion is shown as *gray sphere*. The p.K155 and p.R102 residues in C3b are depicted by *magenta spheres*. Both mutations, p.K155Q and p.R102G, are not positioned at the contact interface of the two proteins. Diagram was generated with the PyMOL molecular visualization system

Discussion

In the present study, we identified 11 missense mutations in six candidate complement (*C3*, *CFB*) and complement regulatory (*CFH*, *MCP*, *CFI*, *THBD*) genes in 13 congenital TTP patients with renal insufficiency and classified them into rare, low frequency, and common mutations.

The rare missense mutation, C3:p.K155Q found in patient ID 1 is located in the macroglobulin-like (MG) 2 domain of C3, where other mutations predisposing to increased complement activation were previously identified. Figure 1 depicts the location of the C3:p.K155 residue in the crystal structure of the complex of C3b and CFH CCP1-4 domains [17]. The p.K155Q mutation is positioned slightly away from the interface between C3b and CFH CCP1-4, making it unlikely that their interactions are directly affected. Prediction of the impact of this mutation by PolyPhen-2 and SIFT showed "benign" and "tolerated"

effects, respectively. For a definite verdict, however, functional studies of the C3:p.K155Q mutation would be needed. In case of common mutation C3:p.R102G, which is also positioned away from the interface between C3b and CFH CCP1-4 (Fig. 1), experimental data indicate that this C3 variant weakly binds to CFH, resulting in reduced CFH cofactor activity thereby favoring alternative complement pathway amplification [21].

The low frequency mutation, CFB:p.L9H within the CFB signal peptide sequence has been reported to be protective for age-related macular degeneration [22]. The low frequency mutation CFB:p.G252S is located in the CFB linker region between the CCP3 domain and the von Willebrand factor A domain. Functional consequences of this mutation are unknown. On the basis of the CFI crystal structure, the low frequency mutation CFI:p.R201S resides on the surface region of the protein away from the proposed cofactor and/or substrate interaction sites, indicating a non-dysfunctional mutation [23]. This mutation is found only in Far East populations including Japanese [19].

The remaining seven mutations found in our cohort are commonly present in the general population. In the study of a rare renal affection, dense deposit disease, both p.R102G and p.P314L mutations in C3 were identified as genetic risk factors for developing this disease [24]. C3:p.R102G is also strongly associated with age-related macular degeneration with an estimated population attributable risk of 22 % [25, 26]. In our cohort, both C3:p.R102G and C3:p.P314L were in perfect linkage disequilibrium and five patients with renal insufficiency carried both mutations (Table 1), pointing to susceptibility for renal involvement through probable hyperactivation of the complement cascade.

Previous functional analyses indicated that the common mutations, CFH:p.V62, C3:p.G102, and CFB:p.R32, are disease-risk mutations [21, 27–29]. The combination of these three mutations yielded sixfold higher hemolytic activity compared to the protective mutations CFH:p.I62, C3:p.R102, and CFB:p.Q32 [21]. The patient with the rare C3:p.K155Q mutation (ID 1) and two other congenital TTP patients with renal involvement (ID 9 and 11) are carriers of the combined disease-risk mutations (Table 1). The CFH:p.E936D mutation in the CCP16 domain of CFH found in congenital TTP patients ID 2, ID 5, ID 11, ID 12 (in homozygous state) and ID 13 (in homozygous state) has been associated with aHUS [30, 31]. Although these common mutations are not extremely destructive, the combined effects of disease-risk mutations as well as the rare missense mutation C3:p.K155Q may influence susceptibility to renal involvement in congenital TTP patients with hereditary ADAMTS13 deficiency.

Two of 13 congenital TTP patients with renal insufficiency carried homozygous deletions of *CFHR1/CFHR3* genes (Table 1). The complete absence as well as barely detectable levels of CFHR1/CFHR3 are related to the occurrence of autoantibodies to CFH [32] that account for 5–10 % of aHUS cases [5]. Therefore, in addition to the above-mentioned missense mutations in complement genes, the deletion of *CFHR1/CFHR3* may contribute to renal affection in congenital TTP patients.

Taken together, our study demonstrates that most of the congenital TTP patients with renal insufficiency do not carry genetic mutations in complement or complement regulatory genes known to predispose to renal insufficiency. Second, although some congenital TTP patients with renal insufficiency were found to be carriers of common aHUS-risk mutations, such as CFH:p.V62, CFH:p.D936, C3:p.G102, CFB:p.R32, and homozygous deletions of *CFHR1/CFHR3* genes, these mutations were not more common than in the general population or in our 19 congenital TTP patients without renal involvement.

Microvascular platelet thrombosis and endothelial injury resulting from ADAMTS13 deficiency initiate the coagulation and fibrinolytic pathways, which in turn may contribute to complement activation in congenital TTP [33, 34]. Complement activation with consumption of complement factors has already been demonstrated during acute TTP episodes [34, 35]. Overactivation of the alternative complement pathway also leads to coagulation cascade activation. Our results suggest that rare predisposing complement genetic mutations do not contribute to a large extent to the phenotypic variability in congenital TTP patients. Further, the common aHUS-risk mutations in complement or complement regulatory genes observed in our small series of congenital TTP patients with renal insufficiency were equally frequent in congenital TTP patients without renal failure. Recruitment of larger number of congenital TTP patients with well-defined phenotypes will be necessary to obtain a full conclusion.

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Compliance with ethical standards

Conflict of interest Dr. Lämmle is a member of the Data Safety Monitoring committee of the BAX 930 Study testing rADAMTS13 in congenital TTP patients. Dr. Fujimura is a recipient of the research fund from Alexion Pharmaceuticals. Other authors have no conflict of interests.

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非典型溶血性尿毒症症候群（aHUS）診療ガイド 2015

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1. はじめに

血栓性微小血管症（thrombotic microangiopathy: TMA）は微小血管症性溶血性貧血（microangiopathic hemolytic anemia、MAHA）、消費性血小板減少、微小血管内血小板血栓による臓器機能障害を 3 主徴とする病態である。代表的疾患として溶血性尿毒症症候群（hemolytic uremic syndrome：HUS）と血栓性血小板減少性紫斑病（thrombotic thrombocytopenic purpura：TTP）が挙げられる。以前は臨床的に消費性の血小板減少症、微小血管での溶血性貧血、急性腎障害の 3 徴を呈する疾患を HUS、さらに発熱、動

揺性精神神経障害を加えた5徴を示す疾患を TTP と診断していたが、両者は臨床症状のみでは鑑別しえないことが多かった。近年両者の病態が解明され、志賀毒素を産生する病原性大腸菌（Shiga toxin-producing Escherichia coli：STEC）によるものを STEC-HUS、ADAMTS13（a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13)酵素活性が 10%未満に著減するものを TTP と診断する。

HUS 症状を呈する患者の約 90%は血性下痢を伴う STEC 感染によるものであるが、残りの約 10%は下痢を伴わず、志賀毒素も検出されないことから、かつては D（diarrhea）(-) HUS と呼ばれた。また 1975 年には家族性の HUS も報告され[1]、これらの STEC 感染を伴わない HUS や家族性の HUS は、非典型溶血性尿毒症症候群（atypical HUS、aHUS）と呼ばれるようになった。1981 年には、兄弟で補体関連因子の一種である H 因子（complement factor H、CFH）の蛋白量の減少を示し HUS を呈する例が報告され、劣性遺伝を示すことから遺伝性の HUS の存在が示唆された[2]。その後、1998 年に Warwicker らの連鎖解析により CFH の遺伝子異常が示され、これが最初の aHUS 遺伝子異常の報告となった[3]。その後、C3 や B 因子（complement factor B, CFB)、I 因子（complement factor I、CFI)、CD46（membrane cofactor protein、MCP)、thrombomodulin (THBD) などの補体関連の遺伝子異常による aHUS、抗 H 因子抗体による aHUS が次々と報告されてきたことから、aHUS は補体関連因子の遺伝子異常による疾患と捉えられるようになった。

本邦では、2008 年に aHUS 患者で初めて CFH の遺伝子異常が報告され[4,5]、その後、次々と aHUS の症例報告がされた。この様な背景から 2013 年に日本腎臓学会と日本小児科学会の合同で、「非典型溶血性尿毒症症候群（aHUS）診断基準」を作成した[6,7]。2013 年の診断基準においては、aHUS を広く定義することで本疾患の認知度を高めることを目的とし、aHUS は大きく「TMA から STEC-HUS と TTP を除外した疾患」であると定義した。従って 2013 年の診断基準では、aHUS は遺伝性の補体制御異常や抗 H 因子抗体によるもの（補体制御異常による aHUS（狭義の aHUS））だけでなく、代謝性、感染症、薬剤性、妊娠関連、自己免疫疾患・膠原病関連、骨髄移植・臓器移植関連の aHUS（以後、二次性 TMA（その他の TMA とも称される）と定義）を含む「広義の aHUS」として定義された。

しかしながら、

1. 国際的には二次性 TMA は aHUS には含まれない方向であること[8,9]

2. 近年、補体関連遺伝子異常だけではなく、凝固系に関連する因子の遺伝子異常も aHUS の原因として判明してきていること

3. 2013 年には補体制御異常による aHUS が抗補体（C5）モノクローナル抗体製剤エクリズマブの適応症に追加されたが、適応症ではない二次性 TMA に対して本薬剤の使用が見受けられたこと

4. 2015 年から非典型溶血性尿毒症症候群が指定難病、小児慢性特定疾病に指定されたが、これは補体制御異常による aHUS を指しており、非典型溶血性尿毒症症候群の定義を見直す必要性が出てきたこと

などを考慮し、本邦における aHUS 診断基準の改訂を行った。また、本改訂版では診断へのプロセス、血漿治療、エクリズマブの使用法などの項目を加え、あらたに診療ガイドとした。今回の診断基準の改訂、診療ガイドが広く臨床の場において活用されることで、本邦における aHUS 診療の質が向上することを願う。

2. TMA と aHUS の定義

TMA はもともと全身諸臓器の微小血管の血栓と、血管内皮障害を呈する病態を総称した病理学的診断名である。これは 1）微小血管症性溶血性貧血、2）消費性血小板減少、3）微小血管内血小板血栓による臓器機能障害を特徴とする病態で、臨床的には破砕赤血球、血小板減少、血栓による臓器機能障害を特徴とする。TMA の病態を示す代表疾患として、TTP、STEC-HUS、補体関連 aHUS、二次性 TMA 疾患が含まれる。TMA の種類により血栓による障害が起きやすい臓器は異なるが STEC-HUS と aHUS は特に腎障害が多い。

aHUS をはじめ、TMA に含まれる疾患の分類に関して、いまだに国際的統一分類がない。2013 年に日本腎臓学会と日本小児科学会から「非典型溶血性尿毒症症候群(aHUS)診断基準」が公表され、aHUS は、微小血管症性溶血性貧血、血小板減少、急性腎障害を 3 徴とし、志賀毒素に関連するものでないこと、TTP でない疾患であると定義された[6,7]（図 1)。

2014 年の Scully らの expert opinion では、aHUS と診断するための除外疾患として、STEC-HUS、TTP の他に、二次性の原因（薬剤性、感染、移植後、コバラミン欠損、全身性エリテマトーデス、抗リン脂質抗体症候群、強皮症など）による TMA を挙げており、これらを除いたものを aHUS と定義している[10]。また 2014 年の George らによる TMA の総説では、aHUS の atypical という用語は歴史的に HUS や TTP に対する用語として用いられたが、aHUS の原因がはっきりしてきたことから aHUS という用語は使用せずに、すべてを TMA と総称し TMA を 9 つに分類することが提唱された。さらに、これまで補体関連 aHUS に分類されていた疾患を、補体関連 TMA と凝固関連 TMA に分類した[11]。しかしながら、George らの分類では遺伝子異常の見つからない患者は補体関連 TMA や凝固関連 TMA に分類できないこと、TMA を呈する疾患全てを TMA とする名称も世界的に浸透しているわけではないこと、また aHUS という病名は本邦で広く使用されていることから、本診断基準改訂版ではこの分類は採用しないこととした。

今回の aHUS 診療ガイドでは、2013 年の本邦の診断基準における先天性、および後天性の補体制御異常による aHUS のみを「aHUS」または「補体関連 HUS」と定義し、TMA の原因となる他の病態による TMA を「二次性 TMA（その他の TMA)」と定義した（図 1）[9,10,12]。

すなわち、本診断基準改訂版での aHUS は、

（1）先天性の補体関連遺伝子異常として、2015 年現在で判明している CFH、CFI、CD46（MCP)、C3、CFB、THBD、 diacylglycerol kinase ε（DGKE）(DGKE は補体系との関連がはっきりしておらず、aHUS に含めない論文もあるが、本診療ガイドでは含めた）の 7 遺伝子異常例（plasminogen（PLG）遺伝子変異の報告もあるが今後の検証が必要である）

（2）後天性の aHUS として抗 H 因子抗体陽性例

（3）TMA を呈し STEC-HUS、TTP、二次性 TMA が否定的で、上記既知の原因遺伝子異常は認められないが臨床的に aHUS が疑われる例

である。なお、TMA を来した病因が明らかな TMA は、病因（原疾患名）と TMA を併記する（例えば肺炎球菌による TMA など)。

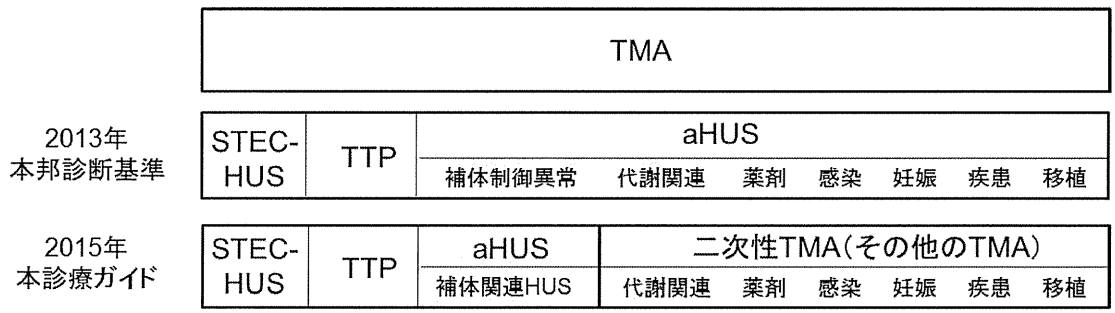


図 1　日本腎臓学会と日本小児科学会による 2013 年診断基準と、本診療ガイドの aHUS 定義の違い

3. 疫学

正確な発症数は不明であるが、海外からの報告では、aHUS は毎年成人 100 万人あたり 2 人、小児では 100 万人あたり 3.3 人発症すると報告されており [13]、18 歳未満の発症が約 40%とされる [12,14]。なお、英国の前向き研究では、約 1 年間の観察で人口 100 万人あたり 0.4 人の発症との報告もある [15]。近年、本邦においても様々な遺伝子異常による aHUS が報告されているが、全国での発症数、原因遺伝子の頻度、予後に関しては不明である。本邦では 2015 年度現在で 100～200 例前後が aHUS と診断されていると推定される。

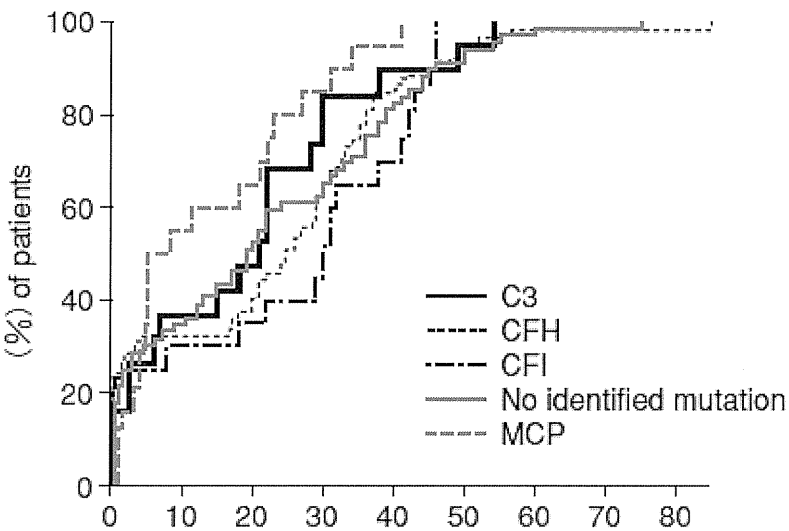


図 2　aHUS の発症年齢（文献 [14] より）

4. 病因・病態

補体関連 aHUS は、補体活性化経路の 1 つである第二経路の異常活性化により発症する。第二経路において、C3 が C3a と C3b に分解されると、生じた C3b が微生物などの細胞膜表面に結合し、B 因子や D 因子等と反応して C3 転換酵素（C3bBb）を形成する。この C3 転換酵素は、さらに C3 を C3a と C3b に分解し、生じた C3b と結合して C5 転換酵素（C3bBbC3b）となる。C5 転換酵素は C5 を C5a と C5b に分解し、

生じた C5b が C6-C9 と順次反応することで膜侵襲複合体（membrane attack complex、MAC）となり、病原体の溶菌・細胞膜融解を引き起こす。

C3 の分解反応により生じた C3b は、病原体だけでなく自己の細胞膜上にも結合しうる。C3b の自己細胞への結合は有害であるため、自己細胞上では H 因子、CD46、THBD などの制御因子を補助因子として、I 因子による C3b の速やかな分解・不活化が促され、補体による細胞傷害から自己細胞を保護している（図3）。

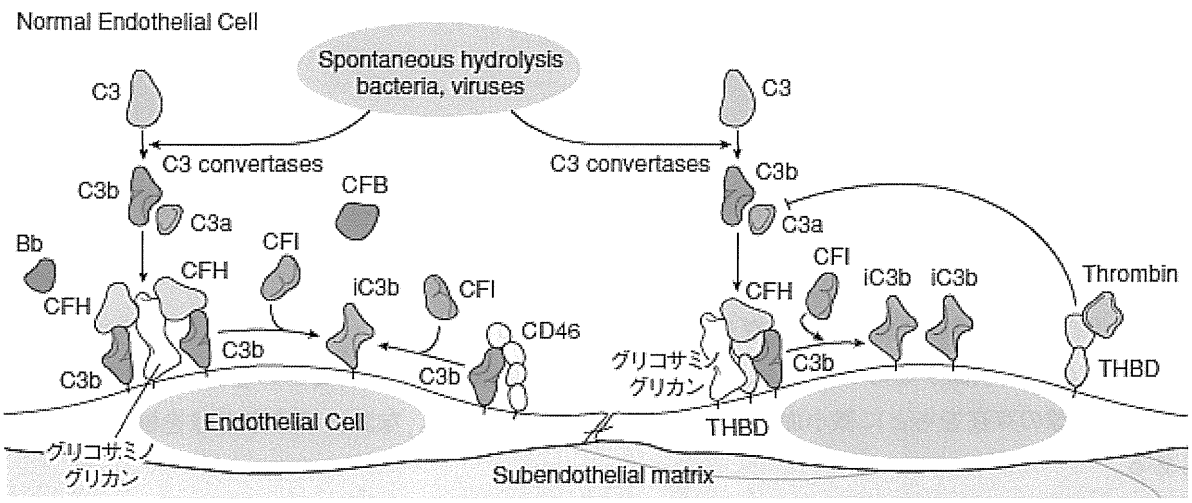


図 3　補体と血管内皮細胞の模式図（文献[16]より）

aHUS は、抑制因子の機能喪失変異と、活性化因子の機能獲得変異に分けられる。抑制因子の機能喪失変異の例として、CFH、CFI、CD46、THBD の変異、または抗 H 因子抗体の出現による H 因子の機能低下が挙げられ、抑制機能の低下により補体系が過剰に活性化されることで aHUS が発症すると考えられる。活性化因子の機能獲得変異の例としては、CFB、C3 の変異が挙げられ、いずれも第二経路の過剰な活性化により血管内皮細胞や血小板表面の活性化をもたらし、aHUS を発症すると考えられる。

aHUS 患者の約 10～20%で H 因子に対する自己抗体の存在が知られており[17]、この抗体は H 因子の C 末端にあるドメインを認識し、H 因子の自己細胞膜表面への結合を阻害することで、H 因子による細胞保護作用を阻害する。抗 H 因子抗体の出現は CFH 関連（Complement Factor H Related、CFHR）1～5 の遺伝子異常（欠損）が関与していることが判明しており、特に CFHR3-CFHR1 が欠損している人に多いとされる。これらの遺伝子異常により H 因子に対する抗体が出現し、H 因子の機能を阻害すると考えられている。

近年、TMA 患者で THBD、DGKE、PLG などの凝固系の制御に関連する因子の異常が報告されているが[18,19]、TMA の発症機序に関してはまだ詳細が分かっておらず、純粋に凝固系異常による TMA なのか、補体系を介した TMA なのかは明確ではない。THBD は、本来は凝固関連因子であるが、C3b や H 因子に結合し、C3b の不活化を促進させることが報告されている。THBD、DGKE、PLG を凝固関連 TMA と呼ぶ分類も提唱されているが[11,20]、本診療ガイドでは THBD と DGKE、（および PLG）を aHUS に含めて解説している。

5. 診断

5−1. 症状

特発的に発症する場合や、感染などを契機に発症することが多いとされる[21]。STEC-HUS と同様に、溶血性貧血、血小板減少、腎不全による症状を認めることが多い。これ以外に中枢神経症状、心不全、呼吸障害、腸炎、高血圧などの多臓器症状を呈することがある。aHUS でも虚血性腸炎などの消化器症状を呈する例や、STEC 以外の細菌やウイルスなどによる消化器感染を契機に aHUS を発症する例もあり、下痢を呈していても aHUS が否定されるわけではないので注意を要する[21]。

5−2. 臨床的診断基準

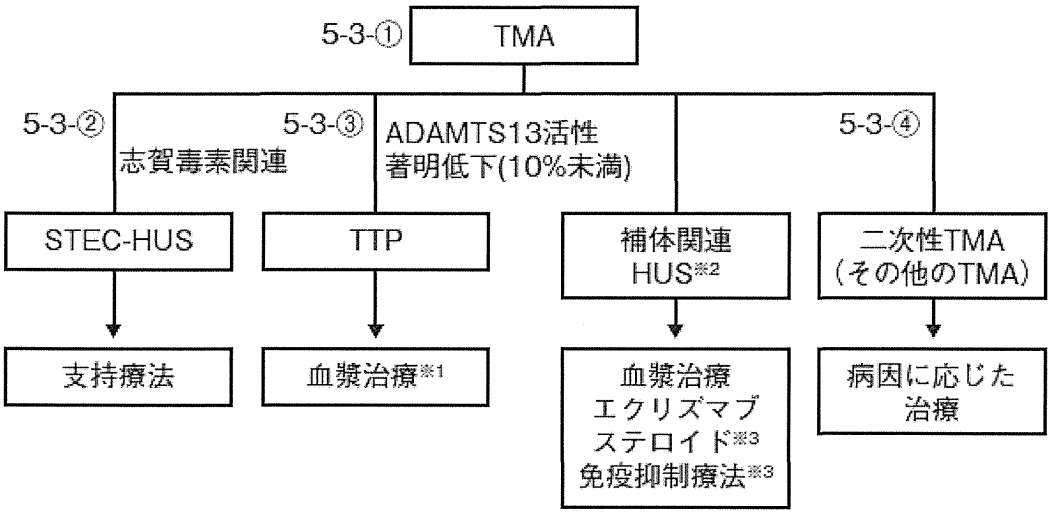
下記の三徴候を認める TMA のうち STEC-HUS、TTP、二次性 TMA（代謝異常症、感染症、薬剤性、自己免疫性疾患、悪性腫瘍、HELLP 症候群、移植後などによる TMA）を除いたものが臨床的 aHUS である。必ずしも三徴候を認めないこともある。

（1）微小血管症性溶血性貧血；ヘモグロビン（Hb） 10g/dl 未満
血中 Hb 値のみで判断するのではなく、血清 LDH の上昇、血清ハプトグロビンの著減、末梢血塗沫標本での破砕赤血球の存在をもとに微小血管症性溶血の有無を確認する。なお、破砕赤血球を検出しない場合もある。
（2）血小板減少；血小板（platelets、PLT） 15 万/μl 未満[12]
（3）急性腎障害(acute kidney injury、AKI)；小児例では年齢・性別による血清クレアチニン基準値の 1.5 倍以上（血清クレアチニンは、日本小児腎臓病学会の基準値を用いる）。成人例では AKI の診断基準を用いる。

5−3. 鑑別診断

TMA の患者を診た際には、まず STEC-HUS や TTP の除外診断を行い、さらに TMA を来す基礎疾患を有する二次性 TMA の除外を行った患者が、臨床的に aHUS と診断される[10,20]。家族歴を聴取し、aHUS と診断された者、aHUS の認知度が低かった時代に HUS や TTP と診断された者、原因不明の腎不全を呈する者、TMA を再発する者などが家族にいる場合には aHUS を強く疑う。なお、aHUS 原因遺伝子異常があっても発症するのは全体で 50%程度とされており、家族歴がはっきりしない例も多い。

必要な検査は、年齢などにより異なるが一般に下記の検査を行う（図 4）。



※1 血漿輸注，血漿交換。
※2 本診断ガイドによるaHUSには，THBD，DGKE異常によるものを含む。
※3 抗H因子抗体陽性例では考慮される。

図 4. TMA 鑑別と治療のフローチャート

① TMA の診断と TMA 類似疾患の鑑別

・溶血性貧血の確認と他疾患の鑑別：LDH の上昇、血液像で破砕赤血球の有無、ハプトグロビン著減の確認、またクームス試験により自己免疫性溶血性貧血を鑑別する。

・急性腎障害を来す他の疾患の鑑別

・播種性血管内凝固症候群（disseminated intravascular coagulation、DIC）の鑑別：PT、APTT、FDP、D ダイマー、フィブリノーゲンなどを測定し、DIC の診断基準などを用いて鑑別する。通常、DIC は敗血症、悪性腫瘍、血液疾患、外傷などの基礎疾患の元で発症する。

・悪性貧血の鑑別：悪性貧血はまれに TMA の様な所見を呈することが報告されており[22]、ビタミン B12、葉酸を測定する。一般的に、悪性貧血では網状赤血球は減少していることが多い。

・ヘパリン起因性血小板減少症（heparin-induced thrombocytopenia 、HIT）の鑑別

② STEC-HUS の鑑別

便培養検査、便中の志賀毒素直接検出法、抗 lipopolysaccharide（LPS）-IgM 抗体などが、STEC 感染を証明するのに有用である。STEC-HUS では血便を約 8 割で認め、血液成分が多い重度の血便を伴い、超音波検査では上行結腸壁の著明な肥厚とエコー輝度の上昇が特徴的で、回盲部から肛門側まで肥厚し、重症例では大腸全体に及ぶことも多い。小児では、STEC-HUS が TMA 全体の約 90%を占めることから、生後 6 か月以降で、重度の血便を主体とした典型的な消化器症状を伴う症例では、最初に考えるべきである。詳細は、HUS ガイドライン(http://www.jsn.or.jp/academicinfo/report/hus2013book.pdf)などを参照。

③ TTP の鑑別

ADAMTS13 活性が 10%未満で ADMAMTS13 に対する中和抗体（インヒビター）が陽性であれば、後天性 TTP と診断する。ADADMTS13 活性が 10%未満で同インヒビターが陰性の場合、先天性 TTP を疑う[23]。先天性

TTP の確定診断には、ADAMTS13 遺伝子解析が必要となる。TTP 以外の aHUS、HUS、二次性 TMA などでも ADAMTS13 活性の軽度低下が認められることがあるが、一般的に活性は 20%以上である[24]。

④　二次性 TMA の鑑別

・コバラミン代謝異常症（特に生後 6 か月未満で考慮）：生後 1 年以内に、哺乳不良、嘔吐、成長発育不良、活気低下、筋緊張低下、痙攣などを契機に発見される例が多いが、近年、成人例の発症例も報告されている。血漿ホモシスチン、血漿メチルマロン酸、尿中メチルマロン酸などを測定する[25]。

・自己免疫疾患・膠原病：全身性エリテマトーデス、強皮症クリーゼ、抗リン脂質抗体症候群、多発性筋炎/皮膚筋炎、血管炎：これらの疾患は TMA を呈することがあるため、必要に応じて以下の検査を提出する。

抗核抗体、抗リン脂質抗体、抗 DNA 抗体、抗セントロメア抗体、抗 Scl-70 抗体、C3、C4、CH50、IgG、IgA、IgM、Anti-neutrophil cytoplasmic antibody（ANCA、抗好中球細胞質抗体）など。

・加速型ー悪性高血圧：ただし、aHUS でも高血圧を呈することが多いので鑑別には注意が必要である。

・悪性腫瘍：進行性の悪性腫瘍により TMA を来すことがある。症例報告をまとめたレビューでは、消化器系癌、乳癌、前立腺癌、肺癌などが多く、9 割以上で転移を認める進行性の悪性腫瘍であったとの報告がある[26]。

・感染症：肺炎球菌感染症の中でも、特に侵襲性肺炎球菌感染症が TMA を呈することがあり、小児に認められる。侵襲性肺炎球菌感染症とは、重症肺炎、髄膜炎、菌血症、敗血症、膿胸等を生じる重症肺炎球菌感染症と定義される。国立感染症研究所の報告では 5 歳未満では本邦で年間 300 例程度の報告がある。TMA 発症は乳幼児が主であり、0.6%程度が TMA を発症するとされる[27,28]。肺炎球菌が産生するニューラミニダーゼによって露出する Thomsen-Friedenreich（T）抗原に対する抗 T-IgM 抗体が血漿中に存在するため、血漿投与により病状が悪化する可能性がある。直接 Coombs 試験が約 90%の症例で陽性を示す[29]。新鮮凍結血漿を用いた血漿交換療法や血漿輸注等の血漿治療や非洗浄血液製剤の投与は行わない。

その他、HIV、インフルエンザ A ウイルス H1N1 亜系、C 型肝炎ウイルス、サイトメガロウイルス感染症、百日咳、水痘、重症溶連菌感染症などが TMA を起こすことが報告されている[21,30,31]。ただし、インフルエンザウイルスなどの感染を契機として aHUS が発症する例もあるので注意が必要である[32]。

・妊娠関連の HELLP 症候群、子癇：HELLP 症候群（妊娠高血圧症に合併する溶血性貧血、肝障害、血小板減少）、子癇（妊娠中の高血圧症とけいれん）は、分娩により速やかに軽快する。ただし、TTP や aHUS でも妊娠を契機に発症する例が報告されており、特に aHUS 患者では分娩後の発症も多いと報告されるが HELLP 症候群においての割合は不明であり、今後の検討課題である[33]。

・薬剤性 TMA：抗悪性腫瘍薬、抗血小板剤、免疫抑制剤などが原因となり、TMA を発症することがある（表 1）[34]。可能であれば被偽薬を減量・中止する。

・急性膵炎：急性膵炎の経過中に TMA を呈することがある[35]。血漿交換が有効との報告がある[36]。

・造血幹細胞・臓器移植後 TMA：造血幹細胞移植後の TMA が特によく知られている。ADAMTS13 活性は 10%未満には著減せず、血漿交換の有効性は低い。一般的には免疫抑制作用を持つカルシニューリン阻害薬の中止、または減量を行う[37]。造血幹細胞移植後の TMA 発症に CFHR3-CFHR1 領域の遺伝子欠損、抗 CFH 抗体を高率に認めたとの報告があるが、今後の検証が必要な課題である[38]。

腎移植後に発症する TMA は、原疾患が aHUS で腎不全に陥った症例の aHUS の再発、腎移植後に新規で発症した aHUS、臓器移植に伴う移植後 TMA が疑われる[34]。aHUS 患者に腎移植を行った場合、TMA の再発と