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Thrombotic Microangiopathy in Children: Pathophysiology, Diagnosis, and Treatment Advances

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Abstract: Thrombotic microangiopathy (TMA) represents a severe clinical condition characterized by endothelial injury, microvascular thrombosis, and multiorgan dysfunction. In pediatric patients with renal involvement, TMA is a significant contributor to morbidity and mortality, demanding prompt recognition and tailored management strategies. This review provides a comprehensive analysis of TMA within the context of pediatric nephrology, encompassing its diverse etiologies, including atypical hemolytic uremic syndrome (aHUS), shiga toxin-associated HUS, and secondary TMA linked to systemic conditions or therapeutic interventions. The article highlights recent advancements in diagnostic techniques, with a focus on biomarkers and genetic profiling, which have enhanced the precision of TMA classification and risk stratification. Furthermore, it examines evolving therapeutic modalities, such as complement inhibitors, alongside traditional interventions like plasma exchange and supportive care. By synthesizing current evidence, this review aims to elucidate the pathophysiological underpinnings of TMA, identify critical gaps in research, and propose future directions to optimize outcomes in renal pediatric patients. The insights offered are poised to inform clinical practice and stimulate further investigations into this complex and life-threatening condition.

Keywords: *Thrombotic Microangiopathy, Renal Involvement*

Introduction.

The evaluation of an adult patient presenting with thrombotic microangiopathy (TMA) requires an initial workup to identify potential causes, including thrombotic thrombocytopenic purpura (TTP) caused by a deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin motif type 1, member 13), Shiga toxin-producing Escherichia coli hemolytic uremic syndrome (STEC-HUS), and secondary forms of TMA associated with infections, medications, malignant hypertension, autoimmune conditions, and other triggers. If these potential causes are excluded, complement-mediated/atypical hemolytic uremic syndrome (CM-HUS or aHUS) should be considered [1–3].

While there is overlap in the etiologies of TMA in adults and children, certain conditions are more prevalent in children, and some rare causes are unique to the pediatric population. In children, the most common cause of

TMA is STEC-HUS, followed by complement-mediated TMA and Streptococcus pneumoniae-associated TMA (Sp-HUS) [4]. Additionally, rare conditions such as congenital TTP, defects in vitamin B12 metabolism (cobalamin C and G defects), and coagulation disorders related to diacylglycerol kinase epsilon (DGKE) mutations can present as TMA. These rare causes often complicate the diagnostic process, particularly in children younger than 2 years. Furthermore, TMA associated with solid organ and hematopoietic stem cell transplantation (HSCT) adds to the complexity of differential diagnosis in pediatric cases.

Although disease-specific registries, such as those for TTP and aHUS, exist, there is a notable lack of TMA registries focusing on young children. A German study reported that among 232 TMA patients, 61% had aHUS [5]. Similarly, in a Brazilian cohort of aHUS patients, 53% of the 17 patients who first manifested symptoms before the age of 18 were younger than 2 years. One patient in this cohort, who was refractory to eculizumab treatment, had a homozygous DGKE mutation [6, 7].

Given the diverse etiologies and potential therapeutic options, a tailored diagnostic approach is critical. This review outlines the causes of TMA—both acquired and inherited—and presents a practical algorithm to guide the diagnosis and management of TMA in pediatric populations.

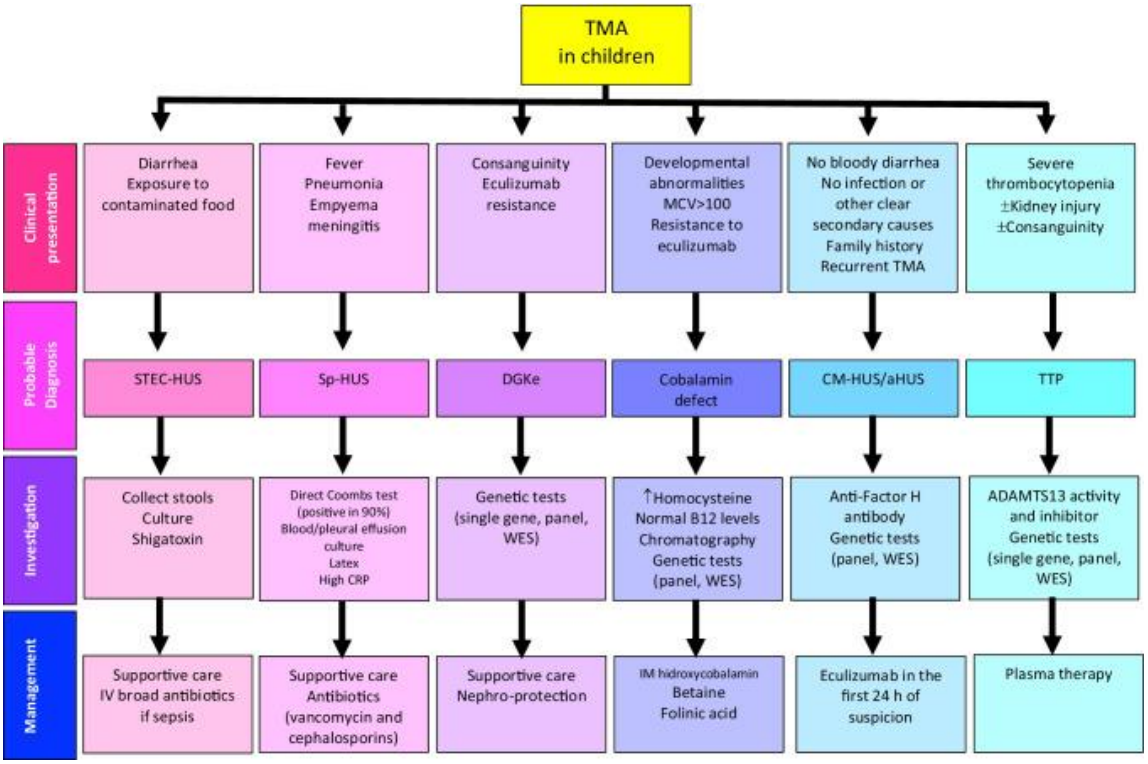

Figure 1: Differential diagnosis of thrombotic microangiopathy in children: singularities of clinical presentation, tools for investigation and a pragmatic approach to management. MCV mean corpuscular volume, STEC-HUS shigatoxin-associated hemolytic uremic syndrome, Sp-HUS Streptococcus pneumoniae hemolytic uremic syndrome, CRP C-reactive protein, DGKe diacylglycerol kinase epsilon, CM-HUS complement-mediated hemolytic uremic syndrome, TTP thrombotic thrombocytopenic purpura, WES whole exome sequencing, ADAMTS13 a disintegrin and metalloprotease with thrombospondin type-1 repeats, 13thmember,TA-TMA transplant-associated TMA [7].

Shiga Toxin-Associated Hemolytic Uremic Syndrome (STEC-HUS)

Incidence and Epidemiology

STEC-HUS is one of the leading causes of acute kidney injury in children [8, 9]. First reported by Gasser et al. in 1955 [10], it is associated with diarrhea caused by Shiga toxin-producing *Escherichia coli* (STEC), affecting an estimated 2.8 million cases globally each year. The incidence of STEC-HUS varies geographically, ranging from

0.5 cases per 100,000 population in Finland [11] to 12 cases per 100,000 in Argentina, where it is endemic [12]. The condition shows seasonal variation, peaking in summer, and primarily affects children under 5 years of age. In this age group, *E. coli* O157 is the most commonly implicated strain in the USA [13]. In Finland, children under 3 years have an increased risk of HUS following STEC infection [11]. A significant outbreak occurred in Germany in 2011, resulting in approximately 4,000 diarrhea cases linked to *E. coli* O104, 845 cases of STEC-HUS, and 54 deaths. Among the 90 pediatric cases, one fatality was reported, and the outcomes mirrored previous series, though most affected children were older than 10 years [14]. Non-O157 *E. coli* serotypes are becoming more prevalent in Europe [15]. A northern Italy study reported a 15.9% incidence of STEC-HUS in patients with Shiga toxin-positive bloody diarrhea [16].

Clinical Presentation and Diagnosis

STEC-HUS is defined by platelet consumption, hemolysis, and acute kidney injury. It often follows a prodrome of bloody diarrhea 2–5 days after STEC infection. Microangiopathic symptoms typically manifest a few days post-diarrhea, occurring in only 10–20% of cases. Extrarenal manifestations may involve the central nervous system, cardiovascular system, gastrointestinal tract, pancreas, and musculoskeletal system [17]. Decreases in complement component 3 (C3) are common in severe cases [18, 19] but usually temporary, reflecting secondary complement activation in vascular inflammation [20]. Reduced C3 levels do not exclude STEC-HUS [21]. Inflammatory markers like C-reactive protein and d-dimer are frequently elevated [22]. Early stool sample collection for culture or PCR is crucial as detection rates decline after the 10th day of diarrhea, with 90% of cultures becoming negative after 15 days [23]. Testing for Shiga toxin in all TMA cases and coordinating with health authorities to access specialized laboratories is critical. When stool samples are negative, serological testing (e.g., IgA, IgG, and IgM antibodies to *E. coli* lipopolysaccharides) can aid diagnosis [15]. For *E. coli* O157, Glyco-iELISA detecting IgM antibodies enhances diagnostic accuracy [24].

A prolonged recovery beyond two weeks necessitates considering aHUS as a differential diagnosis, especially in cases with:

- Negative stool cultures or Shiga toxin PCR beyond 10 days of diarrhea
- Persistent thrombocytopenia without superimposed infection
- Relapsing TMA patterns
- Kidney injury lasting more than 4–6 weeks without septic or hypovolemic shock
- Absence of diarrhea or Shiga toxin test negativity
- Persistently low C3 levels

In these cases, early specimen collection is paramount for accurate diagnosis [4]. Genetic variants in complement genes should be suspected in patients with persistent or recurrent TMA or prolonged low C3 [25].

Pathophysiology

The association between STEC infections and HUS was first described by Karmali et al. [26]. Shiga toxins (Stx1 and Stx2), produced by HUS-inducing *E. coli* strains, are major contributors to endothelial damage. These toxins bind to globotriaosylceramide (Gb3/CD77) in endothelial cell membranes, particularly in the kidneys and brain, causing cellular apoptosis and exposing subendothelial layers, thereby initiating TMA [27]. Toxins also activate pro-inflammatory and pro-thrombotic pathways, exacerbating von Willebrand factor secretion [8].

Management

STEC-HUS treatment is supportive, focusing on patient stabilization. Early volume expansion has been shown to improve renal and neurological outcomes [28]. A systematic review demonstrated no specific therapy surpassing supportive care [13]. Analyses from the 2011 German outbreak highlighted typical clinical progress, with diarrhea resolving in a median of six days and kidney recovery averaging two weeks. Therapies like plasmapheresis, corticosteroids, and eculizumab showed no significant benefit during the outbreak [29–32]. Clinical trials for eculizumab in STEC-HUS are ongoing, though some case reports suggest benefits in specific scenarios, such as late neurological involvement [33, 34]. Fosfomycin may prevent progression to STEC-HUS when administered early in diarrhea onset [35]. Long-term sequelae include proteinuria and hypertension in

approximately 30% of patients [13]. Thus, follow-up with a nephrologist is recommended. Emerging evidence suggests a role for probiotics in prevention and management, warranting further research [36].

Complement-Mediated, Atypical Hemolytic Uremic Syndrome (aHUS)

Incidence and Epidemiology

Atypical hemolytic uremic syndrome (aHUS) is a form of TMA caused by dysregulation of the alternative complement pathway. Recently, the term complement-mediated hemolytic uremic syndrome (CM-HUS) has been introduced, reflecting complement overactivation in conditions previously categorized as secondary TMAs, such as malignant hypertension, which has significant therapeutic implications [37]. For this discussion, aHUS refers to CM-TMA cases without other secondary conditions (primary CM-TMA). It is an ultrarare condition with an incidence of less than one case per million people annually [38].

Approximately 50–60% of aHUS patients exhibit genetic defects or autoantibodies that lead to complement pathway overactivation, though the prevalence of genetic findings varies globally—from 18% in an Indian cohort [39] to 80% in Japan [40]. The introduction of eculizumab, a terminal complement inhibitor, significantly improved outcomes, reducing the progression to kidney failure or death from 30–50% to 9% in children and from 56–67% to 6–15% in adults [41].

Clinical Presentation and Diagnosis

The clinical hallmark of aHUS is the TMA triad: non-immune microangiopathic hemolytic anemia, thrombocytopenia or a marked (>25%) decrease in platelet count, and variable organ injury. Diagnosing aHUS is challenging as there is no definitive test, and it requires exclusion of more common causes of TMA [42], a task complicated by the disease's high morbidity and mortality [43].

A key diagnostic consideration in aHUS is the relationship between genetic findings and clinical presentation. Most patients carry heterozygous genetic variants with incomplete penetrance, often associated with risk polymorphisms and environmental triggers that precipitate full-blown TMA. A 2007 study by the French Society of Pediatric Nephrology found that 52% of children with aHUS had genetic mutations, with complement factor H (*CFH*) mutations associated with worse prognosis and transplant outcomes [44]. Similarly, analysis of 273 patients in the International Registry of Recurrent and Familial HUS/TTP revealed that adults had poorer outcomes compared to children, and familial cases fared worse than sporadic cases. Genetic or risk polymorphisms were identified in 75% of patients, with genotypes varying by ethnicity [43]. Bresin et al. [45] highlighted that combining risk haplotypes in *CFH* and *MCP* with mutations leads to worse outcomes. Data from The Global aHUS Registry, which includes over 800 patients, confirmed that adults and individuals with *CFH* pathogenic variants have worse renal outcomes compared to children [46].

Pathophysiology

aHUS results primarily from dysregulation of the alternative complement pathway. Its association with complement abnormalities was first described in 1981 [47], when siblings from consanguineous families with aHUS were found to have low blood levels of complement factor H (CFH). In 1998, T. Goodship's team linked aHUS to chromosome 1q32, which houses genes for complement regulatory proteins [48].

Subsequent studies identified defects in additional complement regulatory components of the alternative pathway, including loss-of-function mutations in *CD46* (membrane cofactor protein, MCP), *CFI* (complement factor I), thrombomodulin (*THBD*), and *CFHR1–5* (factor H-related proteins 1 to 5 and hybrid genes), as well as *CFP* (properdin). Gain-of-function mutations in *CFB* (factor B) and *C3* genes encoding C3 convertase components have also been described. Anti-factor H antibodies, particularly in children, play a significant role in the pathogenesis of aHUS, with implications for targeted therapy [49].

Understanding the genetic basis of aHUS is essential for prognosis and management. Patients with *CFH* pathogenic variants have worse outcomes, including higher recurrence rates post-kidney transplant. Conversely, those with *MCP* variants or high-risk polymorphisms rarely experience transplant recurrence, though they may have intermittent TMA episodes throughout their lives [46, 50, 51].

Management of aHUS

Understanding the pathophysiology of atypical hemolytic uremic syndrome (aHUS) and identifying specific defects in the alternative complement pathway are crucial for targeted treatment. However, treatment initiation does not require prior genetic test results. In September 2011, the FDA approved eculizumab (Soliris, Alexion) as the first terminal complement inhibitor for use in patients with paroxysmal nocturnal hemoglobinuria (PNH) and aHUS. Studies on eculizumab's efficacy in treating aHUS have shown favorable outcomes in both adults [52–54] and children [55], as reviewed extensively [56].

Nearly a decade after eculizumab's introduction for aHUS [57], debates continue regarding the need for lifelong treatment. A French prospective study involving 57 patients across 22 centers explored eculizumab discontinuation [58]. The trial included patients treated for at least six months who were in remission. Eligibility required either (1) a glomerular filtration rate (GFR) > 60 mL/min/1.73 m^2 (measured via Schwartz or MDRD formulas for children and adults, respectively) and a urinary protein/creatinine (UPC) ratio < 0.05 or (2) stable kidney function over six months. Relapse rates were higher in children (31%) than adults (19%) and in those with pathogenic genetic variants. One exceptional case involved a patient with negative initial genetic tests later found to have a homozygous ADAMTS13 mutation and low plasma ADAMTS13 activity. At two-year follow-up, patients with relapses had worse proteinuria compared to non-relapsing cases. Although discontinuing eculizumab in controlled cases appeared safe, relapse risks should be discussed with patients and caregivers, and eculizumab must remain readily accessible.

Additionally, ravulizumab, a newer long-acting C5 inhibitor, has demonstrated efficacy and safety in phase 3 trials involving adult and pediatric aHUS patients [59, 60].

Streptococcus pneumoniae-Associated Hemolytic Uremic Syndrome (Sp-HUS)

Incidence and Epidemiology

Sp-HUS is a significant cause of thrombotic microangiopathy (TMA) in children, accounting for 5–15% of HUS cases and 1–3% of all TMA cases. Its prevalence has likely increased due to non-vaccine serotypes of *Streptococcus pneumoniae* [61]. The condition predominantly affects children under two years old, with pneumococcal pneumonia/empyema causing 60% of cases and meningitis 30% [62]. Among pneumococcal infections, the progression rate to HUS is 0.4–0.6% [63]. Historical mortality rates were as high as 50%, with 67% of survivors developing chronic kidney disease (CKD) or hypertension. By 2007, intensive care improvements reduced mortality to 12.3% and CKD progression to 16%.

Clinical Presentation and Diagnosis

Sp-HUS typically presents with the TMA triad approximately 7–9 days after pneumococcal infection onset. Differential diagnoses include disseminated intravascular coagulation (DIC) secondary to pneumococcal infection, which may involve altered coagulation parameters and bleeding, unlike TMA. Thrombocytopenia and anuria/oliguria tend to be more prolonged in Sp-HUS compared to shigatoxin-associated HUS (STEC-HUS) [61]. The direct Coombs test is positive in 90% of Sp-HUS cases, distinguishing it from other TMAs [61].

Pathophysiology

Pneumococci secrete neuraminidase, an enzyme that removes neuraminic acid to expose the Thomsen–Friedenreich antigen (T-antigen) on red blood cells, platelets, and glomerular endothelial cells [64, 65]. Preformed IgM antibodies bind to this antigen, triggering hemolysis and endothelial damage. Recent studies have linked decreased sialylation of transferrin and IgA1 O-glycans to the disease's pathophysiology. Neuraminidase also disrupts Factor H function, impeding its regulation of C3 convertase and activating the alternative complement pathway [66].

Management

Management of Sp-HUS focuses on supportive care, including dialysis and prompt antibiotic therapy. Early detection and antibiotic initiation significantly reduce mortality. Severe cases may warrant broad-spectrum

coverage with vancomycin and cephalosporins, adjusted based on culture and sensitivity results. Platelet and red blood cell transfusions should be washed to remove IgM antibodies targeting the T-antigen. While plasma exchange to remove neuraminidase has been proposed, its efficacy remains controversial due to potential exacerbation of microangiopathy. Case reports have noted successful outcomes using eculizumab in severe Sp-HUS cases [67].

Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP)

Incidence and Epidemiology

iTTP is an immune disorder caused by IgG autoantibodies inhibiting ADAMTS13, an enzyme critical for cleaving ultra-large von Willebrand factor (ULVWF) multimers. While more common in adults, iTTP is a life-threatening condition requiring rapid diagnosis and treatment.

Clinical Presentation and Diagnosis

The classic clinical pentad of iTTP includes hemolytic anemia, thrombocytopenia, neurological symptoms, jaundice, and fever, though complete presentation is rare [68]. To differentiate iTTP from other TMAs, the Harvard TMA Research Collaborative developed the PLASMIC score, which includes factors such as platelet count, hemolysis, absence of active cancer or transplant history, mean corpuscular volume < 90 fL, normal coagulation, and creatinine < 2.0 mg/dL [69]. This bedside scoring system reliably predicts severe ADAMTS13 deficiency.

Pathophysiology

In the 1980s, ULVWF multimers were identified in TTP patients [70]. These multimers promote platelet adhesion and aggregation by binding to platelet glycoproteins and FVIII. ADAMTS13 degrades ULVWF into smaller, less thrombogenic fragments by cleaving the A2 domain [72]. Severe ADAMTS13 deficiency (<10% activity) leads to excessive ULVWF, microthrombi formation, and resultant ischemia. The HLA variant rs6903608 has been associated with iTTP onset and relapse in Italian cohorts [74].

Management

Untreated iTTP has a 95% mortality rate, often within 24 hours [75]. Rapid initiation of plasma exchange is critical, achieving an 80% response rate and >90% survival if started within 4–8 hours [76]. Fresh frozen plasma can be infused until plasma exchange becomes available, though less effective [77]. Corticosteroids (e.g., prednisone or methylprednisolone) should accompany plasma exchange. Daily exchanges continue until platelet counts exceed 150,000/mm^3 [78].

Recently, caplacizumab, a nanobody targeting von Willebrand factor, has shown efficacy in reducing acute exacerbations when combined with plasma exchange and immunosuppression [80, 81]. While thrombotic events outweigh bleeding risks, platelet transfusions should be reserved for severe bleeding [76].

Hereditary Thrombotic Thrombocytopenic Purpura (hTTP)

Incidence and Epidemiology

Hereditary thrombotic thrombocytopenic purpura (hTTP), also known as Upshaw–Shulman Syndrome [82], is a rare condition accounting for approximately 10% of all TTP cases. It is caused by homozygous or compound heterozygous mutations in the ADAMTS13 gene and is more common in offspring of consanguineous parents. Individuals with simple heterozygous mutations typically show no clinical abnormalities. Diagnosis often shows a bimodal distribution: 50% of cases occur in early childhood (ages 2–5 years), while the remainder are diagnosed later, frequently triggered by pregnancy in young women [78].

Clinical Presentation and Diagnosis

hTTP is characterized by recurrent episodes of microangiopathic hemolytic anemia and thrombocytopenia, often accompanied by neurological symptoms or other organ damage. Diagnostic criteria include severe ADAMTS13 deficiency (plasma activity <10%) in the absence of inhibitory antibodies, confirmed by identifying a pathogenic ADAMTS13 mutation. A diagnostic delay is common. Data from the Hereditary TTP Registry [83]

indicate a mean age of symptom onset of 4.5 years and a mean age of diagnosis of 16.7 years, highlighting a significant diagnostic gap for this condition.

Pathophysiology

Unlike immune-mediated TTP (iTTP), where antibodies inhibit ADAMTS13 activity, hTTP results from a genetic deficiency of ADAMTS13. This deficiency prevents the cleavage of ultra-large von Willebrand factor (ULVWF) multimers, leading to platelet aggregation and microthrombi formation. These platelet-rich microthrombi obstruct small blood vessels, causing ischemia and characteristic TMA findings such as thrombocytopenia and schistocytes. ADAMTS13 levels can vary based on the specific mutation, which impacts disease severity and clinical presentation [78].

Management

Treatment involves regular plasma infusions of 10–15 mL/kg every 21–28 days to supply functional ADAMTS13.

Thrombotic Microangiopathy (TMA) Mediated by Cobalamin Defects

Incidence and Epidemiology

Inherited vitamin B12 metabolism disorders, such as cobalamin C deficiency (cblC; OMIM #277400), increase the risk of TMA. This condition typically presents in neonates or infants during the first year of life with symptoms of methylmalonic aciduria and homocystinuria [84]. Clinical features often include failure to thrive, hypotonia, seizures, microcephaly, and developmental delays. In Brazil, three cases were diagnosed, with one revealing two novel pathogenic MTR variants through whole-exome sequencing, indicating methionine synthase deficiency (MSD) [85]. Adult cases are rare but have been reported, presenting with anemia, thrombocytopenia, and renal dysfunction [86, 87].

Clinical Presentation and Diagnosis

In infants, cobalamin defects manifest as failure to thrive, seizures, hypotonia, and neurological delay. Adults may exhibit cognitive impairment, ataxia, or psychosis. Laboratory findings often include hyperhomocystinemia, low plasma methionine, and methylmalonic aciduria. TMA-associated symptoms include anemia, thrombocytopenia, acute kidney injury, and hypertension. Chronic kidney disease (CKD) with hypertension and proteinuria affects up to 40% of cases.

Pathophysiology

Mutations in MMACHC (chromosome 1p34.1) disrupt cobalamin metabolism by impairing the synthesis of methylcobalamin and adenosylcobalamin. This leads to homocysteine and methylmalonic acid accumulation, which promotes endothelial damage, platelet aggregation, and thrombosis. These metabolic disruptions result in the characteristic microangiopathic findings of TMA [1].

Management

The standard treatment is parenteral hydroxycobalamin (1 mg intramuscularly daily) [86], which prevents progression to renal failure and other microangiopathic complications. Testing for homocysteine and vitamin B12 levels is recommended in TMA patients, especially those with neurological symptoms, macrocytosis, or resistance to complement inhibitors.

TMA Mediated by Diacylglycerol Kinase Epsilon (DGKE) Mutation

Incidence and Epidemiology

DGKE mutations, an ultrarare non-complement-mediated cause of TMA, were first described in 2013 through whole-exome sequencing [88]. While incidence data remain unclear, these mutations are linked to autosomal recessive inheritance patterns.

Clinical Presentation and Diagnosis

Loss-of-function mutations in DGKE present clinically with a spectrum ranging from membranoproliferative glomerulonephritis to steroid-resistant nephrotic syndrome and HUS [89, 90]. Patients often have proteinuria, hematuria, and hypertension, with slow progression to CKD. Mutation screening is recommended for TMA

cases beginning in the first year of life, particularly with consanguineous parentage or poor response to complement inhibitors.

Pathophysiology

DGKE encodes an enzyme involved in converting diacylglycerol (DAG) to phosphatidic acid, essential for lipid signaling. Loss of DGKE activity disrupts endothelial cell and platelet homeostasis, inducing a prothrombotic and inflammatory state. Early-onset disease is attributed to endothelial apoptosis and impaired angiogenesis. Unlike complement-mediated TMA, DGKE-related TMA does not recur after kidney transplantation.

Management

Treatment options, including plasma exchange, plasma infusion, and immunosuppression, have shown inconsistent results. Recurrence is noted even with complement inhibitors like eculizumab [42]. Current strategies focus on nephroprotection, including strict blood pressure control and renin-angiotensin-aldosterone system blockade.

Transplant-Associated TMA (TA-TMA)

Incidence and Epidemiology

TA-TMA arises from endothelial injury in recipients of solid organ or hematopoietic stem cell transplantation (HSCT). Its pathophysiology involves multiple factors, including ischemia-reperfusion injury, calcineurin inhibitor toxicity, antibody-mediated rejection, infections, and complement dysregulation. Among HSCT recipients, the cumulative incidence is approximately 3% [92].

Clinical Presentation and Pathophysiology

TA-TMA typically presents with hemolysis and platelet consumption, often preceded by hypertension. Kidney involvement is mild and late. In solid organ transplants, differentiating TA-TMA from conditions like antibody-mediated rejection or calcineurin toxicity is critical. Genetic variants in complement genes may underlie susceptibility.

Management

Short-course eculizumab has shown promise in improving survival, with one cohort reporting an increase in 1-year post-HSCT survival from 16.7% to 66% [93]. Early recognition and complement inhibition are crucial when aHUS recurrence is suspected.

Conclusion

Accurate diagnosis and identification of the underlying etiology of thrombotic microangiopathy (TMA) in children are essential for effective disease management. In children under 2 years old, the causes of TMA vary and include common entities such as Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome (STEC-HUS) and atypical hemolytic uremic syndrome (aHUS). Less frequent causes include *Streptococcus pneumoniae*-associated HUS (Sp-HUS), immune-mediated thrombotic thrombocytopenic purpura (iTTP), and hereditary TTP (hTTP). Rare conditions such as cobalamin C deficiency-mediated TMA (cblC-TMA) and diacylglycerol kinase epsilon mutation-associated TMA (DGKE-TMA) also contribute to the spectrum.

TMA associated with solid organ or hematopoietic stem cell (HSC) transplantation involves a multifactorial pathophysiology, and these cases may also include additional underlying complement dysregulation. Early and precise diagnosis of the specific TMA subtype is critical, as treatment strategies, prognosis, and patient outcomes are highly dependent on timely initiation of targeted therapies.

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