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PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

The Complement Alternative Pathway and Preeclampsia

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Abstract

Purpose of Review Significant and intricate immune adaptations are essential for the establishment and maintenance of normal pregnancy. Preeclampsia is a morbid, potentially life-threatening disease for both mother and neonate that occurs uniquely in pregnancy, at least in part, due to maternal immune maladaptation. We aim to review the literature that focuses on case reports, diagnostic approaches, and treatment strategies for disorders of the complement alternative pathway (CAP) as related to preeclampsia.

Recent Findings There is evidence of complement dysregulation in preeclampsia and HELLP syndrome, similar to that observed in a few rare types of thrombotic microangiopathies. Complement dysregulation may be identified with functional laboratory testing as well as genetic testing.

Summary Increased utilization of a standardized diagnostic approach to establish whether persistent and/or severe cases of preeclampsia and HELLP syndrome are complement-mediated may lead to development of future treatment strategies, such as complement-targeted therapy.

Keywords Preeclampsia · HELLP syndrome · Complement · Alternative pathway · Complement genetic variants

Introduction

Preeclampsia is a potentially life-threatening disease characterized by new-onset hypertension and proteinuria or other evidence of end-organ damage, occurring in the latter half of pregnancy. Other evidence of end-organ damage that may occur in preeclampsia includes, but is not limited to, pulmonary edema, renal dysfunction, and eclampsia [1••]. Hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is a descriptive term of a constellation of findings occurring in a pregnancy and is considered a "severe feature" and variant of preeclampsia. Table 1 outlines the diagnostic criteria of preeclampsia. Preeclampsia-related adverse outcomes occur antepartum, intrapartum, postpartum, and long-term in affected women and their offspring. In the twenty-first century, the pathogenesis continues to be poorly understood, and thus, preeclampsia still remains an incurable disease.

Maternal–Placental Immune Tolerance and Immune Maladaptation

Significant and intricate immune adaptations occur in pregnancy to maintain a competent immune system to fight off disease, meanwhile preventing rejection of the fetus, which is an allograft containing paternal antigens. This phenomenon is referred to as the maternal–placental immune tolerance [2]. The physiologic changes are numerous. There is a shift of maternal immune response from T-helper 1 to T-helper 2 type cytokine profile [3]. T cell activation is overall suppressed, and natural killer cells are downregulated by macrophages and syncitiotrophoblasts partly through the expression of the enzyme indoleamine-2,3-dioxygenase [4, 5]. There is an increased number of granulocytes in maternal blood as well as increased concentration of acute-phase proteins. Additionally, increased concentrations of the complement system anaphylatoxins C3a and C5a are observed [6]. In summary, pregnancy can be characterized

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Table 1 Criteria for diagnosis of preeclampsia

Blood pressure	Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 h apart after 20 weeks of gestation in a previously normotensive patient
	If systolic blood pressure is ≥ 160 mmHg or diastolic blood pressure is ≥ 110 mmHg, confirmation within minutes is sufficient
AND	
Proteinuria	≥ 0.3 g in a 24-h urine specimen or
	Protein/creatinine ratio ≥ 0.3 mg/mg (30 mg/mmol)
	If quantitative measurement is unavailable: dipstick ≥ 1+
OR	
In the absence of proteinuria, new onset of elevated blood pressure as described above plus any one of the following:	
Thrombocytopenia	Platelet count < 100,000/μL
Renal insufficiency	Serum creatinine > 1.1 mg/dL (97.2 μmol/L) or doubling of the creatinine concentration in the absence of other renal diseases
Impaired liver function	Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
Pulmonary edema	
Cerebral or visual symptoms	For example, new-onset and persistent headaches not responding to usual doses of analgesics; blurred vision, flashing lights or sparks, scotomata

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by enhancement of the innate immune system and suppression of the adaptive immune system.

The complement system is a central component of the innate immune system and a regulator of tissue homeostasis. Three different pathways can activate the complement cascades: classical, alternative, and lectin/mannose-binding [7]. Figure 1 illustrates the complement cascade. Each pathway is activated by different threats or pathogen patterns, and therefore, the recognition molecules which trigger activation of each pathway differ. The classical pathway is activated by an antigen–antibody immune complex or C-reactive protein (CRP), whereas the lectin pathway is activated directly by mannose-containing bacterial surfaces. The complement alternative pathway (CAP) is always active at low levels, in a surveillance role, and can be initiated by spontaneous hydrolysis of C3. All three pathways converge to a C3-mediated amplification loop by pathway-specific C3 convertases. The activation of C3 by the C3 convertases generates C3b, a fragment that will bind and tag foreign cell or bacterial surfaces. This step leads to the terminal pathway of complement with the main goal of cell lysis. The formation of the C5 convertase with C3b initiates the formation of the so-called membrane attack complex (MAC) or C5b-9, which when anchored to the cell surface creates a pore promoting membrane rupture and cell lysis. In addition to the formation of the MAC, the anaphylotoxins C3a and C5a, which have potent inflammatory effects and promote chemotaxis, are generated after C3 and C5 cleavage, respectively [8].

Complement activation is controlled by a set of membrane-bound and fluid-phase regulators to prevent over-activation. Complement factor H (CFH) is a fluid-phase inhibitor which regulates the CAP activation to prevent damage to self. It competes with factor B (CFB) for binding to C3b and acts as a cofactor for factor I (CFI) to inactivate C3b to iC3b, and it also enhances the dissociation of the CAP C3 convertase. Any imbalance between the acting and regulatory mechanisms caused by genetic variants or acquired autoantibodies, such as anti-complement factor H antibody, to the complement components may trigger disease processes, frequently fueled by inflammatory and thrombotic routes [9].

There are many theories attempting to explain the pathogenesis behind preeclampsia, such as abnormal placentation, immunologic maladaptation, genetic factors, and endothelial dysfunction [2, 10••, 11••, 12]. One well-accepted theory is of immune maladaptation. The immunologic maladaptation theory in women affected by preeclampsia was partly evidenced when prior exposure to paternal antigens deemed the woman more "immune" to preeclampsia, i.e., at decreased risk for preeclampsia [12–14].

Thrombotic Microangiopathy and the Great Imitators

Thrombotic microangiopathy (TMA) is defined by the occurrence of thrombi in microvasculature of several organs, leading to thrombocytopenia, mechanical microangiopathic

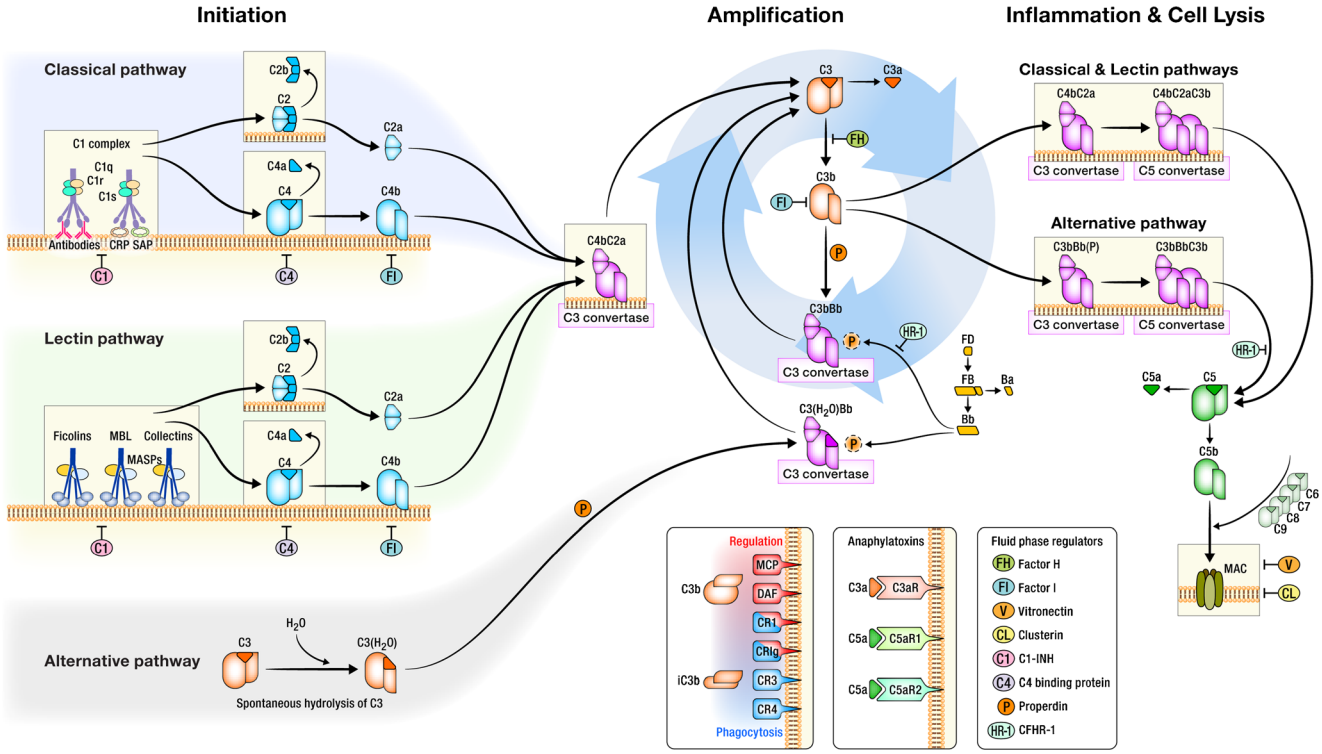

Fig. 1 The complement cascade. The complement cascade is made up of three pathways, ultimately converging into a common pathway (Figure is copyrighted by the Mayo Clinic and is reproduced with their permission.)

hemolytic anemia, and organ failure. TMA is notable for causing specific abnormalities in the microvasculature, the arterioles, and capillaries, which is the underlying cause of hemolytic anemia. The clinical presentation of hypertension, thrombocytopenia, and renal injury is quite similar to that of HELLP syndrome, serving as evidence that HELLP syndrome is a form of thrombotic microangiopathy [15•]. Although renal biopsies are not commonly performed in HELLP syndrome, case reports show that renal biopsy in this clinical setting is consistent with the underlying pathology of TMA [16]. However, severe hypertension, usually a prominent feature of HELLP syndrome, may also cause secondary TMA and yield similar histological results.

The CAP is implicated in certain rare TMA syndromes, such as the atypical hemolytic uremic syndrome (aHUS). The pathophysiologic mechanism of aHUS involves increased and unregulated hydrolysis of complement component C3 to C3b, leading to tissue deposition of C3b, formation of the MAC, and subsequent cell lysis and tissue injury. The most common underlying susceptibility factors include germline mutations in complement proteins and regulators or acquired autoantibodies against complement regulators. This results in failure to protect the affected tissue from complement activation, causing TMA, and often, renal failure [17, 18].

Clinically, there are some "great imitators" of preeclampsia whose underlying pathophysiologic mechanisms involve TMA, as outlined in Table 2 [19]. In fact, an international consensus statement published in 2016 indeed classifies TTP, aHUS, and HELLP syndrome all under the umbrella of TMA.

Evidence of Complement Dysregulation in Preeclampsia

The case for complement dysregulation as a central component of preeclampsia, particularly HELLP syndrome, is getting stronger as new studies emerge. Red cell hemolysis in HELLP syndrome can be attributed to mechanical injury in response to complement dysregulation in both the classical and alternative pathways [20, 21••]. Sera from women with HELLP syndrome and preeclampsia have shown evidence of CAP activation. Complement components C5a and C5b-9 were elevated in sera of patients with hypertensive cases when compared to controls; however, it was the increased urinary excretion of C3a and C5a that differentiated preeclampsia from chronic hypertension [22•]. Early gestation serum elevations of C3a and Bb in women prior to the development of preeclampsia give a clue of the role of early complement activation in the disease [23, 24].

Preeclampsia has long been thought to be a placental disease, and delivery of the placenta, in most cases, essentially cures the disease. Abnormal placentation may be related to

Table 2 Clinical signs and symptoms of the great imitators of preeclampsia

Signs and symptoms	HELLP syndrome (%)	AFLP (%)	TTP (%)	HUS (%)	Exacerbation of SLE (%)
Hypertension	85	50	20 to 75	80 to 90	80 with APA, nephritis
Proteinuria	90 to 95	30 to 50	With hematuria	80 to 90	100 with nephritis
Fever	Absent	25 to 32	20 to 50	NR	Common during flare
Jaundice	5 to 10	40 to 90	Rare	Rare	Absent
Nausea and vomiting	40	50 to 80	Common	Common	Only with APA
Abdominal pain	60 to 80	35 to 50	Common	Common	Only with APA
Central nervous system	40 to 60	30 to 40	60 to 70	NR	50 with APA

HELLP, hemolysis, elevated liver enzymes, low platelets; AFLP, acute fatty liver of pregnancy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; APA, antiphospholipid antibodies with or without catastrophic antiphospholipid syndrome; NR, values not reported; common, reported as the most common presentation

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defective decidualization, implantation, and angiogenesis. Animal studies have shown placental complement activation subsequent to decidual angiogenesis, by identifying local misexpression of vascular endothelial growth factor (VEGF) thereby causing complement deposition, ultimately leading to aberrant trophoblast invasion and placentopathy [11••]. C5a deposition in macrophages and C5a receptor overexpression have been appreciated in preeclamptic placentas [25•]. Fetal cord blood was found to have increased levels of Bb in fetuses born to preeclamptic mothers when compared to normotensive controls [10••]. This evidence of complement activation and the maternal–placental interface is suggestive of the role of complement in trophoblast dysfunction in this disease.

Laboratory Studies in Complement Alternative Pathway Dysfunction

Serological complement testing is an important tool to the hematology and nephrology practices when working out a differential diagnosis of TMAs. Different institutions have developed serological panels to detect CAP dysregulation. A reliable panel should include measurements of complement function, complement factor concentrations, complement activation products, and autoantibodies to complement factors, such as anti-factor H antibody, to correctly assign any complement dysregulation to the appropriate pathway [26••]. Since complement activation may manifest in several scenarios, the specificity of any single complement test is low and a panel of tests is preferred. Final diagnosis of TMAs is established clinically, and in many cases, with the support of genetic testing; however, in some institutions, it may take months before a genetic test panel result is reported, and waiting for results to institute therapy is frequently not feasible.

There is international consensus that when diagnosing aHUS, other causes of TMA must be ruled out until finally reaching a point where aHUS is most likely. For example, atypical HUS is usually a diagnosis of exclusion made only after excluding Shiga toxin, diarrhea-positive HUS, and testing for ADAMTS13 activity (a disintegrin and metalloproteinase with a thrombospondin type 1 motif that cleaves von Willebrand factor). ADAMSTS13 activity should be above 10% to rule out thrombotic thrombocytopenic purpura (TTP), another TMA [27•].

Serologic measurements are influenced by time of collection and ideally should be obtained prior to plasma exchange. CAP activation is evidenced in the laboratory by decreased total complement function or decreased measurement of alternative pathway function. In addition, decreased concentrations of the early components of the CAP, such as C3, CFB, or CFH, are possible, signaling extensive depletion of the components of the cascade due to excess activation or poor inhibition or control. Conversely, the complement activation fragments or activation products, such as Bb (a stable fragment of Factor B), C3a, C5a, or the MAC, will be elevated, signaling extensive cleavage of the complement components. Similar patterns may be observed in HELLP/preeclampsia cases when the complement cascade is over-active and CAP dysregulation happens.

Genetic Variants and Autoantibodies Related to CAP

Often, variants of uncertain significance (VUS) are found after complement genetic testing. Several in silico modeling software exist to predict the pathogenicity of a VUS; however, in those cases, the recommendation from the American College of Medical Genetics is that all results have to be correlated with serologic functional and quantitative studies, and when possible, clinical phenotype [8, 28•]. Over 400 variants have

been described for the complement related system, and over 100 genetic variants have been associated with aHUS. The proposed mechanism of aHUS follows the two-hit hypothesis: the first hit is a germline genetic predisposition, and the second hit is a triggering event, such as pregnancy, malignancy, or infection.

Variants in complement related genes have been found to be associated with 50 to 60% of aHUS cases, most of which are heterozygous [18]. The known mutations include gain-of-function mutations of complement pathway activators (*C3* and *CFB*) and loss-of-function mutations of regulators (*CFH, CD46, CFI*, and thrombomodulin (*THBD*)). Although rare, patients with homozygous variants in the *CFH* gene are more likely to exhibit abnormally low serum CFH.

When it came to genetic testing of complement-related genes in HELLP syndrome, studies are not as promising. A case series had previously demonstrated genetic variants in complement-related genes, namely in *CFH*, *CFI*, and *MCP*, in 4 out of 11 patients with HELLP syndrome [29•]. However, another more recent and larger series showed that only 3 out of 33 women with HELLP syndrome carried similar genetic variants, concluding that the genetic predisposition to CAP dysregulation is less prevalent and therefore probably has less of an impact on pathogenesis of this disease than originally thought [30]. Larger-scale studies should be conducted in a heterogeneous population to aid in the understanding of the role of complement-related genetics on preeclampsia. In that context, one may hypothesize that due to overlap between the conditions, the disease-causing variants that cause aHUS can also be pathogenic in the setting of HELLP/preeclampsia, and the two-hit theory also may be applied.

Less commonly, development of anti-CFH autoantibodies has been implicated in less than 10% of aHUS cases and is strongly associated with deficiency in expression of *CFHR1*/*CFHR3* genes, a predisposing factor in aHUS development [31, 32]. Despite the high degree of future relapse, *CD46* variants were consistently found to be associated with higher remission rate and better prognosis in contrast to patients harboring *CFH* or *CFI* variants, who have poor prognosis. Approximately 60% of patients with *CFH* or *CFI* variants will have end-stage renal disease or die within a year. Close to 80% have disease recurrence or graft failure following renal transplantation [33].

What Is the Clinical Significance of Complement in Preeclampsia?

With evidence of complement activation, complement-targeted therapy is an intriguing prospect. Eculizumab is a medication approved by the US Federal Drug Administration for treatment of aHUS, paroxysmal nocturnal hemoglobinuria (PNH), and refractory myasthenia gravis, diseases known to be associated with CAP abnormalities. It is a recombinant humanized IgG2/IgG4 kappa monoclonal antibody that selectively targets and inhibits the terminal portion of the complement cascade, by binding to the complement component C5. But what is the role of this drug in preeclampsia?

Eculizumab's efficacy in preeclampsia was demonstrated in vitro in one study that noted evidence of complement dysregulation in preeclampsia and HELLP syndrome when compared to normal pregnancies and non-pregnant controls. The same study also noted decreased in vitro cell killing when adding eculizumab to HELLP sera, further endorsing the complement dysregulation aspect to these diseases [34••].

There have been multiple reports of use of eculizumab in pregnancy for aHUS and PNH without significant apparent adverse outcomes to mother or fetus, suggesting its safety during this sensitive time [35–37]. The complement system does not appear to be altered in the newborn of a mother treated with eculizumab [38]. Thus far, only a single report of eculizumab treatment of a patient with HELLP syndrome has been published. The diagnosis of HELLP syndrome was made at 26 weeks' gestation, and treatment appeared to prolong pregnancy by 17 days, likely leading to much improved neonatal outcomes [39••]. Although the drug appears to be safe, studies are necessary to evaluate its utility and efficacy in the treatment of preeclampsia prior to its use for this specific indication, since continuous blockage of the complement system by eculizumab leads to a 1000-fold increased risk of meningococcal infections even after vaccination [40•].

Traditionally, prior to the discovery of eculizumab, plasma exchange (PLEX) was the treatment of choice for aHUS. Patients with autoantibodies may respond better than others, which was noted in one series of patients with anti-CFH autoantibody [41]. The study found that patients with high levels of anti-CFH autoantibody had low C3, but normal levels of CFH. Certainly, PLEX is the treatment of choice for TTP. Plasma exchange in preeclampsia, especially in HELLP syndrome, has been used in the past with varying degrees of success [42–44].

Serological testing for CAP components, function, and autoantibodies can help support and justify the utilization of eculizumab on a case-by-case basis, especially when results are abnormal. Eculizumab is considered one of the most expensive drugs in the world, with an annual cost of over $500,000 (USD). Before covering such large expenses, health insurance companies may require strong evidence that the disease is complement-mediated and that the patient will benefit from a therapy with eculizumab. Variants in complement-related genes, if discovered, can help with guiding counseling and in the future, potentially risk stratification. However, the current evidence does not, by any means, support a case for counseling against pregnancy in a nulliparous woman whose mother is known to have a heterozygous complement

regulatory gene variant, especially considering the lack of specificity of the findings and potential overlap with many other complement-mediated conditions.

Current Management of Preeclampsia and HELLP Syndrome

Preeclampsia and HELLP syndrome remain terminal and progressive diseases during pregnancy, and, at this time, the only chance at a real cure is delivery. The current approach per national guidelines, including the American College of Obstetrics and Gynecology (ACOG), is to effect delivery in HELLP syndrome once the diagnosis is made after maternal stabilization, regardless of gestational age [1••]. The timing of delivery in preeclampsia depends on severity, ranging from immediate upon diagnosis to 37 weeks' gestation. Once there is evidence of end-organ damage, ACOG recommends delivery regardless of gestational age. The only time expectant management may be undertaken in case of preeclampsia with severe features is if the only diagnostic criteria met is elevated blood pressure, and if that can be controlled with oral antihypertensive medications, and only until achieving 34 weeks' gestation.

Ultimately, preeclampsia/HELLP syndrome is a clinical diagnosis. Since there is no objective diagnostic test to detect this disease and the symptoms overlap with other diseases, such as the imitators, a definitive diagnosis in most instances cannot be made until after delivery, when prompt resolution of the disease should ensue. Following delivery, if no improvement is noted in the first few days, other differential diagnoses, such as TTP and aHUS, should be entertained and sought after. In aHUS, evidence suggests that prompt treatment is of utmost importance to prevent complications; however, that is not always possible since this diagnosis is a difficult one to make in the clinical setting where preeclampsia is a much more common diagnosis [45]. However, the diagnosis cannot be made unless it is considered. In cases of HELLP syndrome that are severe and persist without improvement for more than 48 h after delivery, assessment of altered complement pathway function may reveal complement-mediated TMA and assist in the final diagnosis.

Future Directions and Conclusion

A very heterogeneous disease, the etiology of preeclampsia is not one that we can currently explain with just one mechanism. Discovery of the etiology for preeclampsia and HELLP syndrome will certainly be a great step towards finding a treatment. Preeclampsia and HELLP syndrome and their maternal and neonatal sequelae directly contribute to the current healthcare economic burden. Related long-term psychosocial and health effects on both mother and child are great. More studies are needed to establish if HELLP syndrome and other forms of preeclampsia are in fact complement-mediated TMA. Our review illustrates that there is evidence the underlying etiology of preeclampsia/HELLP syndrome is, at least in part, related to complement dysregulation. Future research should also focus on establishing a prediction tool to identify those who would benefit from complement-targeted therapy. That is, which patients with preeclampsia/HELLP syndrome have an underlying pathophysiology related to complement dysregulation, so that in the future we can find a cure to this currently incurable, potentially devastating and life-threatening disease, allowing prolongation of pregnancy and avoidance of long-term morbidity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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