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Atypical Hemolytic Uremic Syndrome: Can We Deal With It Today?

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare disease that causes a thrombotic microangiopathy (TMA). The reason for aHUS development is a chronic, uncontrolled activity of the alternative complement pathway. In most cases it is related to genetic defect of regulatory proteins. Diagnosis is based on TMA verifying (triad of microangiopathic hemolytic anemia, thrombocytopenia and renal failure). Distinguishing aHUS from other possible causes of TMAs is essential for an appropriate therapy choice. Diagnostic and treatment possibilities for aHUS have improved significantly last years, including the first drug available for patients with aHUS – eculizumab. However, there are still a lot of problems to be solved by medical community, such as looking for more robust biological markers of aHUS or developing of new drugs.

KEYWORDS

Atypical Hemolytic Uremic Syndrome, Thrombotic Microangiopathy, Eculizumab, Alternative Pathway

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INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare life-threatening multisystemic disorder, which occurs at any age from neonatal period to the adult age, and leads to thrombotic microangiopathy (TMA) [1, 2]. Worldwide, the prevalence of aHUS ranges from 2.7–5.5 per million population with an incidence of about 0.40 per million population. Mortality rates range from 10–15% in the acute phase of the disease and, within a year of diagnosis, up to 70% of patients progress to end-stage renal failure and need dialysis, or die. One patient in 5 has aHUS affecting organs other than the kidneys, most commonly the brain or heart [3].

During the last 10-15 years, a great progress has been made in understanding of pathogenesis of aHUS. Also a pathogenethicaly justified therapy has been available since 2011, when Food and Drug Administration (FDA) approved the use of eculizumab for the treatment of patients with aHUS. Despite the fact that aHUS can lead to life threatening conditions, some patients with aHUS still remain undiagnosed [3]. Problems with distinguishing aHUS between other TMAs and insufficient awareness of clinicians about aHUS could be among possible reasons as well. So, can we deal with such a severe disease today?

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MAIN BODY

Terminology

The name of aHUS has been historically used in medicine to describe HUS that is not related to Shiga-toxin (Stx) producing Escherichia coli (STEC) or Shigella dysenteriae. Nowadays most authors, including ourselves, use the term of aHUS to designate only a complement-related HUS [4] thrombocytopenia and renal impairment. Atypical HUS (aHUS. This form of patalogy will be the main subject of our article.

Etiology and pathogenesis

As mentioned above, the reason of aHUS development is a complement system defect, which leads to chronic uncontrollable activation of complement. Such defects can be either inherited or acquired, and they lead to platelet, leukocyte, and endothelial-cell activation and systemic thrombotic microangiopathy [5–7].

Complement system is activated by three possible pathways: the classical pathway, the lectin pathway, and the alternative pathway [8]. Opposite to the first two, the alternative pathway does not require a

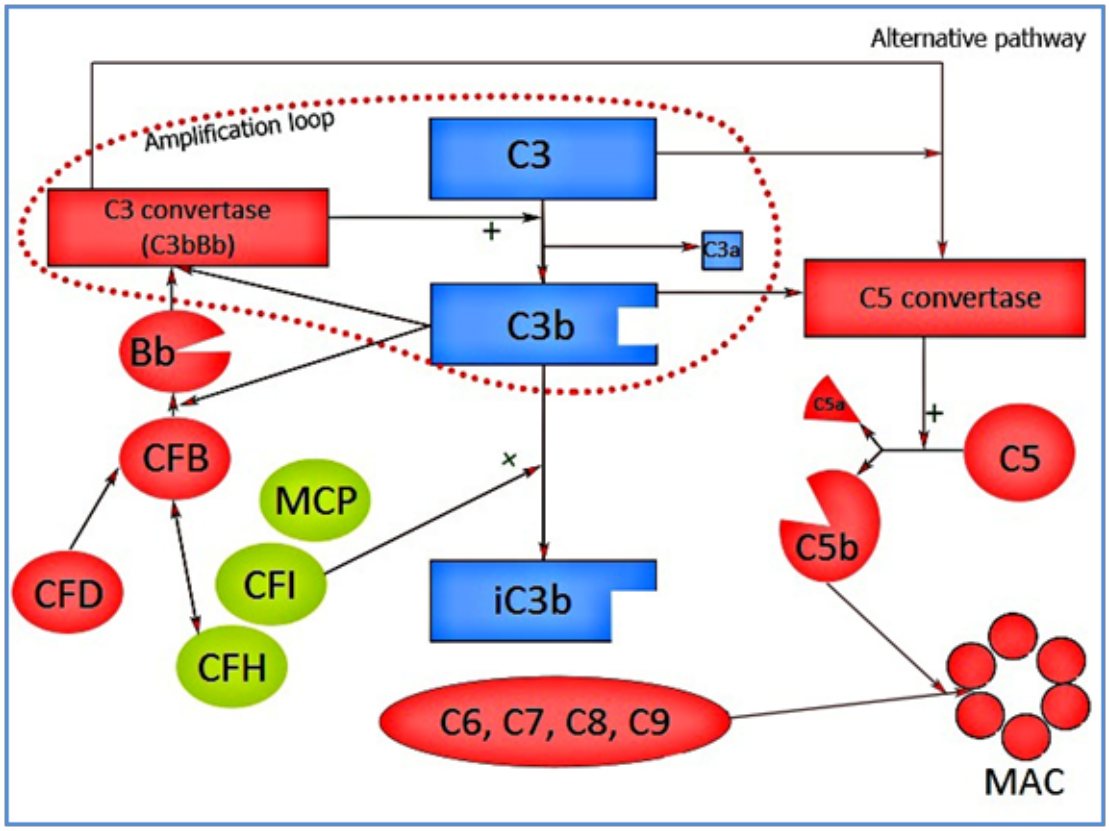

Fig.1. Alternative complement pathway (simplified version)

pathogen to be activated. This pathway is continually activated and spontaneously cleave C3 factor with formation of C3a and C3b. In its turn C3b is able to form C3 convertase, which enhances cleavage of C3 to C3a and C3b (amplification loop). To be generated C3 convertases requires C3b and two complement factors – complement factor B (CFB) and complement factor D (CFD). However, in a normal condition this reaction is strictly controlled by other regulatory proteins of complement system: factor H (CFH), factor I (CFI), membrane cofactor protein (MCP). For example, CFH can compete with CFB for binding C3b, and also it is a cofactor for CFI, which cleaves C3b to its inactive form - iC3b. If C3b is not inactivated, then it can participate in C5-convertase formation. This convertase cleaves C5 with C5b formation that is an important part of membrane attacking complex (MAC). According to this, an activation of C5 is essential for the development of aHUS [10]. Possible regulatory proteins defects and C3 "gain of function" mutation that can lead to aHUS development are shown in Figure 2 [4, 7]thrombocytopenia and renal impairment. Atypical HUS (aHUS.

Diagnosis and differential diagnosis

Diagnosis is based on classical triad of TMA: microangiopathic hemolytic anemia, thrombocytopenia, and renal failure [9]. Microangiopathic hemolytic anemia is diagnosed if haemoglobin ≤ 100 g/dL and should be confirmed by detection of increased serum lactate dehydrogenase, a marked decrease in serum haptoglobin levels, and the presence of red blood cell fragments (schistocytes) in a peripheral blood smear. Thrombocytopenia is defined as a platelet (PLT) count of ≤150,000/lL. For establishment of acute kidney injury (AKI) clinicians are recommended to use the last available criteria of AKI.

The next step for making a diagnosis is to exclude trombotic thrombocytopenic purpura (TTP) and STEC-HUS, the other two conditions that can also lead to trombotic microangiopathies (TMA). For this purpose activity of ADAMTS13 (only decrease of ADAMTS13 activity ≤ 5% is significant for TTP) should be evaluated and Stx/ETEC tests to be performed. It is also recommended to exclude other possible reasons of non-STEC-HUS.

Genetic analyses to identify any mutations that are significant for aHUS development and evaluation of serum complement activity are also available now [6]. Full list of recommended investigations is shown

GENE OR SUBGROUP	PROTEIN AFFECTED	MAIN EFFECT	FREQUENCY (%)
CFH	Factor H	No binding to endotheli um	20-30
CFHR1/3	Factor HR1, R3	Anti–factor H antibodies	6
MCP	Membrane cofactor protein	No surface expression	10-15
CFI	Factor I	Low level or low cofactor activity	4-10
CFB	Factor B	Gain-of-function mu tation. C3 convertase stabilization	1-2
C3	Complement C3	Resistance to C3b inacti vation	5-10
THBD	Thrombomodulin	Reduced C3b inactivation	5

Fig.2. Complement abnormalities and its characteristics. Adapted from [4, 6]

	Investigations
1. STEC infection	Stool or rectal swab: culture for STEC (Mac Conkey for 0157:H7); PCR for Stx Serum: anti-LPS antibodies against the most common serotypes in the local country
2. Disorders of complement regulation C3, C4 (plasma/serum)	Factor H, Factor I, Factor B (plasma/serum) Anti-factor H autoantibodies MCP (surface expression on leucocytes (polynuclear or mononuclear leucocytes by FACS) Gene mutation analysis in factor H, factor I, MCP, C3, factor B
3. ADAMTS13 deficiency **inherited or acquired classification**	Plasma ADAMTS13 activity or dosage (Elisa) ± inhibitor
4. Cobalamin metabolism: methyl malonic aciduria	Plasma amino-acid chromatography (high homocysteine, low methionine); urine organic acid chromatography (methyl-malonic aciduria) ± mutation analysis in MMACHC gene
5. HIV	Serology
6. Pregnancy, HELLP syndrome	Pregnancy test, liver enzymes. Investigate as in 2 and 3
7. Drug induced	Identification of the drug
8. Bone marrow transplant, organ transplant	Anamnesis of transplantation
9. Miscellaneous	Antinuclear antibody, lupus anticoagulant, anti-phospholipid antibodies

Fig.3. Investigations recommended for patients with aHUS. Adapted from [4, 9–11]

Dosage	Regimen
900 mg	weekly for the first 4 weeks
1200 mg	for the fifth dose 1 week later
1200 mg	every 2 weeks thereafter

Fig.4. Recommended dosage regimen for patients ≥ 18 years old [3]

in Figure 3 [9-11].

Treatment

Since 1980s and until recently plasmatherapy (usually plasma exchange) has been a cornerstone and the only option for aHUS treatment. In 2011 Food and Drug Administration (FDA) approved eculizumab for the treatment of patients with aHUS. Eculizumab (Soliris, Alexion Pharma) is a human monoclonal antibody that binds to complement C5 and blocks its cleavage to C5b, preventing the formation of MAC and proinflammatory peptide C5b. A drug has shown its efficacy and safety in clinical trials with 100 patients in total, including trials with children's participation of age from 1 month to 17 years [3], [12].

Since blocking of terminal complement activation pathway increases the risk of meningococcal infection, vaccination against N. meningitidis should be completed before therapy with eculizumab. Also, in some countries patients are given prophylactic antibiotics for a treatment period [13].

It is controversial whether life-long continuous treatment with a complement inhibitor such as eculizumab is required for all aHUS patients. Further studies are needed to clarify this problem.

Recommended dosage regimen for patients 18 years of age and older is shown in Figure 4 [3].

It is worth mentioning that Soliris therapy is extremely expensive. It is the most expensive drug in the world now [14]. Average annually cost for one patient is about 340000$. Surely, it is impossible for most people to provide themselves with eculizumab during the whole life. But since aHUS is an orphan disease some countries have national programmes for supporting such people and supply them with Soliris [10].

New complement blockers that work only at the endothelium surface and do not block complement in the fluid phase might become available in future. Also, recombinant regulatory factors such as CFH are being under development [15–17].

CONCLUSION

In conclusion, we would like to mention that a significant leap in understanding of aHUS has happened within last years. Through the studies in pathogenesis of aHUS new diagnostic methods have been embedded in clinical practice. Such methods are helpful for diagnosing and consequently - for starting an immediate therapy for patients with aHUS. As soon as eculizumab was approved as a treatment, aHUS prognosis for patients has significantly improved. In accordance to the mentioned above, the answer to the question: "Can we deal with aHUS today?" is "Yes, definitely". However, there are still a lot of problems to be solved. In particular, there is still no evidence based guidelines regarding diagnostics and management of patients with aHUS. The other possible direction for further studies is searching for more robust biological markers of aHUS. Another priority is development of the new groups of drugs and their cheaper analogs.

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