

Atypical haemolytic uraemic syndrome

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Abstract

Introduction

Atypical haemolytic uremic syndrome is a result of a spectrum of diseases. Disorders of complement regulation are the most important reasons in the aetiology. It is associated with defective regulation of the alternative complement pathway in over 50% of cases. Clinical abnormalities are related with the presence of thrombotic microangiopathy. Patients with atypical haemolytic uremic syndrome have a poor prognosis with a high mortality and morbidity in the acute phase of the disease and progression to end-stage renal disease in 50% of the cases. Various extra renal complications due to systemic thrombotic microangiopathy may occur in HUS, including neurological, pancreatic and cardiac involvement. Eculizumab is a humanized monoclonal anti-C5 antibody. It blocks the alternative complement pathway at the level of proinflammatory C5a and lytic C5b-9 complex generation. We discuss haemolytic uremic syndrome and treatment options.

Conclusion

Related to increase of experiences, eculizumab therapy may be the first-line treatment. We do not know optimal duration of eculizumab therapy. We do not know also in which patient a severe relapse could be developed. At this moment we can suggest that in both cases eculizumab is life-saving and enhancing the quality of life.

Introduction

Haemolytic uremic syndrome (HUS) is defined by the association of

haemolytic anaemia, thrombocytopenia, and acute renal failure. This life-threatening syndrome is a result of a spectrum of diseases. Clinical abnormalities are related with the presence of thrombotic microangiopathy (TMA).

TMA is characterized by endothelial cell activation, the release of von Willebrand factor, platelet activation and aggregation, leucocyte recruitment, and a procoagulant state¹. Escherichia coli (STEC)-HUS accounts for over 90% of cases, and usually results from infection with STEC². Atypical HUS (aHUS) accounts for 5–10% of cases. Atypical HUS is a heterogeneous disease.

Disorders of complement regulation are the most important reasons in the etiology of aHUS. Defective ADAMTS 13 function, genetic deficiency of thrombomodulin, defective cobalamine metabolism, HIV, pregnancy, malignancy, systemic lupus erythematosus, antiphospholipid syndrome, and quinine or calcineurin induced HUS are others causes of HUS³ (Table 1).

Patients with aHUS have a poor prognosis with a high mortality and morbidity in the acute phase of the disease and progression to end-stage renal disease in 50% of the cases⁴. We discuss haemolytic uremic syndrome and treatment options.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Pathogenesis of aHUS

Atypical HUS is associated with defective regulation of the alternative complement pathway in over 50% of cases. Mutations in the genes encoding the complement regulator factor H (CFH), membrane cofactor protein (MCP: CD46), complement factor I (CFI), thrombomodulin, factor B, C3 or autoantibodies to factor H have been reported to predispose to aHUS. All of these changes results with over-activation of the alternative pathway^{5,6}.

Defective regulation of the complement activation leads to excess generation of cytotoxic C5b-9 and anaphylatoxins C3a and C5a. Membrane attack complex causes cytotoxicity of endothelial cell, intimal swelling and cellular proliferation. This event exposes prothrombotic components in the subendothelial space and causes activation of the coagulation system and fibrin deposition. Microvascular stenosis may also result directly from endothelial swelling and subendothelial expansion.

Abnormal vascular permeability mediated by C3a and C5a may cause interstitial oedema of the brain and other vital organs. Mental changes, seizures, cardiac dysfunction/arrest, pericardial effusion, dyspnoea, pleural effusion, pulmonary infiltration,

Table 1: Aetiology of Atypical Haemolytic Uremic Syndrome

• Disorders of complement regulation (Mutations in complement regulators and complement activators)
• Defective ADAMTS 13 function
• Genetic deficiency of thrombomodulin
• Defective cobalamine metabolism
• HIV
• Pregnancy
• Malignancy
• Systemic lupus erythematosus
• Antiphospholipid syndrome
• Quinine or calcineurin induced

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abdominal pain, nausea, vomiting, diarrhoea, pancreatitis, oedema and renal failure can occur⁷. C3 level may be normal or low. Low levels of complement C3 may indicate this complement dysregulation in aHUS but it is not a definite indication⁸.

Genetic in aHUS

Mutations have been identified in approximately 50-70% of patients, including genes encoding complement regulators (CFH, CFI, complement factor H-related proteins (CFHR), and MCP) and complement activators (complement factor B (CFB) and C3)². Many different mutations in complement genes have been reported, the downstream consequence of them all is over-activation of the alternative complement pathway, excessive liberation of different cleavage fragments from C3 and C5 and formation of the lytic C5b-9 complex. This leads, in turn, to platelet activation, endothelial damage, inflammation and systemic microangiopathic lesions⁹.

CFH is the most important fluid-phase regulator of the alternative pathway. It acts on the proteolytic inactivation of C3b, competes with factor B for C3b binding, and accelerates the decay of C3 convertase into its components. CFH also regulates complement on host surfaces⁵.

Most CFH mutations associated with aHUS are heterozygous, it has been postulated that these mutations may exert a dominant negative effect¹⁰.

Deficiency of CFH related plasma proteins and autoantibody-positive form of HUS (DEAP-HUS) is another sub-group of HUS. It is characterized

by the combination of an acquired and a genetic factor. The acquired factor is autoantibodies to the CFH. These antibodies develop on a genetic background, which is mostly based on a homozygous chromosomal deletion of the CFH1 and CFH3 genes. Autoantibodies in DEAP-HUS, as well as CFH mutations in aHUS that are located within the C-terminal recognition region interfere with surface binding. Mutant CFH show reduced or absent binding which results in a reduced protection of cellular host surfaces and membranes¹¹.

A mutation in membrane cofactor protein (MCP: CD46) is present with low C3b-binding and cofactor activity. MCP mutations are more frequent in children than in adults. C3 levels in MCP-mutated patients are most often normal. Some of the MCP-mutated patients with decreased C3 levels have another mutation responsible for the activation of the complement in the fluid phase⁹.

Complement factor I (CFI) mutations induce a default of secretion or disrupt its cofactor activity, with altered degradation of C3b/C4b in the fluid phase and on surfaces¹². Inactivation of C3b and C4b through limited proteolytic cleavage, results with prevention of the formation of the C3 and C5 convertases and thus down-regulates the alternative and classical pathway⁵. Plasma C3 level is decreased in 20-30% of patients and CFI level in one third of patients⁹.

Mutation in complement factor B (CFB) is also demonstrated. These mutations induce an increased stability and activity of the C3 convertase. It results with increased complement deposition on glomerular

endothelial cells¹³. C3 is the main component of the complement cascade. It plays a central role on the activation of classical and alternative pathways. Most C3 mutations induce a defect of the ability of C3 to bind to MCP. Plasma C3 concentrations are low in 70-80% of patients⁹.

Thrombomodulin induce the activation of protein C by thrombin. It also plays a role on inactivation of C3a and C5a.

Mutations of thrombomodulin result in a loss of cofactor activity¹⁴. Various combinations of 2 or more mutations were demonstrated in 12% of patients with aHUS⁹.

Medical history and rapid laboratory tests are sufficient for aHUS diagnosis. Genetic screening is helpful but it is not necessary for treatment planning. Genetic findings may influence long-term management of patients¹⁵.

Extrarenal Involvements in aHUS

Various extra renal complications due to systemic TMA may occur in HUS, including neurological, pancreatic and cardiac involvement¹⁶.

Neurological involvement is the most frequent extrarenal complication in HUS. Neurological complications, which are a major cause of morbidity and mortality, affect 10-48% of aHUS cases. The pathophysiology of CNS dysfunction can be multifactorial, and may involve multifocal TMA, metabolic insults (uraemia, hypo-natraemia, and hypocalcaemia), uncontrolled hypertension or focal toxin-mediated mechanisms¹⁷.

Complement activation, and subsequent C5a generation, is thought to play a significant role in the progression of CNS disease¹⁸. Posterior reversible encephalopathy syndrome (PRES)-related lesions, are believed to be due to vasogenic oedema and are

Table 2: Eculizumab dosing schedule in aHUS.

Body weight	Week	Induction phase				Maintenance phase				
		1	2	3	4	5	6	7	8	9+
40 kg and over	Infusion (mg)	900	900	900	900	1200	-	1200	-	1200
	Week	1	2		3	4	5	6	7+	
30 kg to <40kg	Infusion (mg)	600		600	900	-	900	-	900	
20 kg to <30 kg	Infusion (mg)	600		600	600	-	600	-	600	
	Week	1		2	3	4	5	6+		
10 kg to <20kg	Infusion (mg)	600		300	-	300	-	300		
5 kg to <10 kg	Infusion (mg)	300		300	-	-	300	-		
	Week	1		2	3	4	5	6+		

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associated with posterior white matter hyperintensity (predominantly in parieto-occipital regions). Systemic thrombotic microangiopathy in the cerebral region can show intensities in many different regions of the brain by MRI¹⁷. Both scenarios produce similar clinical manifestations, including vision loss. One can hypothesize that the two scenarios are interrelated in the case of aHUS as the oedema in PRES can be caused by TMA and uncontrolled complement activation and excessive C5a would increase vascular permeability to further exacerbate oedema¹⁹. While MRI findings are helpful for diagnosing neurological complications and guiding treatment, it is worth noting that there may be a delay between symptom onset and development of radiological signs¹⁷.

Therapy choices in aHUS

In contrast to typical HUS, aHUS is characterized by frequent relapses. Plasma therapy was considered the first-line therapy for patients during the acute episode of aHUS and should be started within 24 hours of diagnosis²⁰. However, in clinical practice, this is not always possible.

Plasma therapy is not successful in all patients. Patients become dependent or resistant to plasma therapy. The necessity of life-long treatment in patients who are dependent on plasma therapy could result with reactions to plasma; worsen school performance and social life. The morbidity and mortality of catheter placement and plasma exchange are also important issues and most studies suggest that plasma therapy often fails to rescue kidney function²¹.

Recently in patients who are resistant to plasma therapy combined kidney–liver transplantation, a high-risk procedure, was the last alternative. Combined kidney–liver transplantation should not be performed unless a patient is at high risk for life-threatening complications²². It has recently been shown that eculizumab is also an effective therapy in aHUS. Eculizumab is a humanized monoclonal anti-C5

antibody. It blocks the alternative complement pathway at the level of proinflammatory C5a and lytic C5b-9 complex generation. Recent case reports have shown that eculizumab may be beneficial in the long term treatment of aHUS²³.

Eculizumab has a high potential in this area. The use of eculizumab over the long term has an extremely high cost, and the time of interrupt is unpredictable but it is a rescue therapy for aHUS. Also eculizumab has a successful effect on the recovery of the renal function. Legendre et al. reported that five of the seven plasmapheresis resistant dialysis patients became free of dialysis²⁴.

Eculizumab should be administered at the recommended dosing interval (Table 2). In all aHUS patients, an eculizumab serum concentration of ~50–100 µg/mL is required to provide complete inhibition of terminal complement activity²⁵.

Eculizumab should be considered for all patients without waiting for results from complement investigations, although screening for anti-CFH antibodies should be done rapidly as positive results would indicate a switch to plasma exchange and immunosuppressive drugs¹⁵.

Screening for genetic complement abnormalities is needed for individualized management. aHUS patients receiving eculizumab therapy should be monitored for TMA by measuring platelet counts, serum lactate dehydrogenase and serum creatinine. aHUS patients may require dose adjustment within the recommended 14 ± 2 day dosing schedule during the maintenance phase. Bacterial infections should be treated promptly according to local treatment guidelines.

Vaccination may not be sufficient to prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected and treated with appropriate antibiotics if necessary. Severe TMA complications have been observed in aHUS patients after eculizumab discontinuation²⁵. The issue of the optimal duration of

eculizumab treatment has not yet been exactly known. Treatments could be individualized on the basis of complement genetics. Life-long treatment may be necessary in patients who have mutations associated with poor outcomes. In the absence of other contraindications, patients with aHUS-related end-stage renal disease should be considered as eligible for renal transplantation after a thorough genetic-based assessment of their risk of recurrence.

Kidney transplantation from a living-related donor can be considered with extreme caution in rare situations but remains inadvisable if the donor shares a genetic susceptibility factor with the recipient or if no mutations have been identified in complement genes.

Prophylactic eculizumab therapy should be recommended in patients with a high risk of post-transplantation aHUS recurrence and should be initiated prior to surgery at day deceased donor transplantation and include an additional dose at day one. After these administrations, eculizumab must continue weekly²⁶.

Conclusion

aHUS is a result of a spectrum of diseases. Disorders of complement regulation are the most important reasons in the aetiology of atypical haemolytic uremic syndrome. Related to increase of experiences, eculizumab therapy may be the first-line treatment of aHUS. We do not know optimal duration of eculizumab therapy. We do not know also in which patient a severe relapse could be developed. At this moment we can suggest that in both cases eculizumab is life-saving and enhancing the quality of life.

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