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# STRATEGIC TOOLS FOR DIAGNOSING ATYPICAL HAEMOLYTIC URAEMIC SYNDROME IN A VARIETY OF THROMBOTIC MICROANGIOPATHY. I: STEPS FOR DIAGNOSIS.

**Dra. Rita Marcela Fortunato**

**Unidad Renal del Hospital Universitario Fundación Favaloro. Cátedra de Nefrología y Medio Interno del Hospital de Clínicas José de San Martín, Universidad de Buenos Aires.**

**Servicio de Nefrología del Hospital Alemán de Buenos Aires. Argentina**

**rfortuna @ ffavaloro. org**

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Comment of the reviewer Carlos G. Musso, MD. PhD. Nephrology Division. Hospital Italiano de Buenos Aires, Argentina.

Comment of the reviewer Susana Gabriela Pérez MD. Especialista en Nefrología. Posgrado de Efectividad Clínica, Analista de Datos Médicos en Diaverum. Argentina.

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**RESUMEN:** La microangiopatía hrombótica es una lesión histológica, la cual asociada con anemia hemolítica no inmune (Coombs negativa) y trombocitopenia conforman el síndrome hemolítico urémico, una tríada de riesgo que es compartida por el Síndrome Urémico Haemolítico Atípico (SHUa) (un trastorno hereditario), el Síndrome Urémico Haemolítico (SHU típico) conocido también como Escherichia coli productora de toxinas Shiga (STEC), pero también por una variedad de condiciones amplificadoras del complemento que hacen necesario establecer estrategias desafiantes para el diagnóstico.

El diagnóstico diferencial entre HUS y trombocitopénica trombocitopénica (TTP) sigue siendo también un paso esencial cuando el paciente se presenta con la tríada descrita. Es de notar que las condiciones amplificadoras del complemento, denominadas como SHU secundarias, pueden en algunos casos enmascarar un SHUa.

Este artículo tiene como objetivo revisar las herramientas disponibles y los pasos que deben considerarse para establecer la causa certera de la tríada para el diagnóstico final de SUH a.

**PALABRAS CLAVE:** Síndrome hemolítico urémico atípico. Microangiopatía trombótica, diagnóstico. ADAMTS 13-13. Complemento. Toxina shiga. Trombocitopenia.

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**SUMMARY:** Thrombotic microangiopathy (TMA) is a histological lesion, which associated with non-immune hemolytic anemia (Coombs negative), and thrombocytopenia conform the haemolytic uraemic syndrome, a life threatening triad shared by Atypical Haemolitic Uremic Syndrome (a hereditary disorder) typical Haemolitic Uraemic Syndrome also known as Shiga toxin-producing Escherichia coli (STEC), but also a variety of amplifying complement conditions that make necessary to establish challenging strategies for diagnosis.

The differential diagnosis between HUS and Thrombotic Thrombocitopenic Purpura (TTP) continues to be also an essential step when the patient present with the triad described. It is worth mentioning that amplifying complement conditions, named as secondary HUS may in some cases mask a aHUS.

This article aims to review the tools available and the steps that must be considered in order to set up the certain cause of the triad for the final aHUS diagnosis.

**KEY WORDS:** Atypical haemolytic uraemic syndrome. Thrombotic microangiopathy, diagnosis. ADAMTS 13-13. Complement. Shiga toxin. Thrombocytopenia.

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## INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is considered an ultrarare disease. It can be induced by genetic alterations that cause abnormalities in regulating factors of the complement pathway on cell surfaces causing systemic lesions of microangiopathy. However, it can be determined by acquired factor (autoantibodies against Facto H) in few cases[1].

There is very few data regarding aHUS incidence and prevalence, but it has an annual incidence of 1-2 cases / million inhabitants in the United States of America[1,2]. In Europe, a recent multicenter international study has seen an incidence of 0. 11 cases / million inhabitants whose ages were between 0-18 years, although unpublished results mention a frequency of 2 to 3 cases/ million[3,4]. The beginning of this entity is more frequent before the age of 18 (60 vs. 40%), with a similar sex distribution, but it may appear at any age[1].

Thus familial aHUS accounts for less than10% of all cases of aHUS, being both dominant and recessive autosomal forms of inheritance observed. Autosomal recessive HUS often occurs early in childhood, its prognosis is poor, recurrences are frequent, and its mortality rate is 60-70%, while dominant autosomal HUS often occurs in adults, with a poor prognosis, and a risk of death or ESRD of about 50-90%[5, 6].

The haemolytic uraemic syndrome (HUS) is characterized by three serious manifestations: non-immune hemolytic anemia (Coombs negative), thrombocytopenia, and acute renal failure, and it is caused by glomerular injury induced through thrombotic microangiopathy (TMA)[2].

TMA is a histological lesion of the vascular wall of arterioles and capillaries, which present intraluminal platelet thrombosis and partial obstruction of their light[2].

The triad described for aHUS is also shared by typical HUS (tHUS) which accounts for 90% of cases of HUS. Although typical HUS is almost exclusively caused by an enteric infection due to Shiga toxin-producing Escherichia coli (STEC) or other verotoxin-producing germs (VTEC), resulting in what is known as tHUS. Clinically, tHUS usually begins with abdominal pain and diarrhea, with acute renal failure developing within 4-10 days. The prognosis is usually good: mortality <5% and complete clinical recovery is achieved in 80% of patients[1-3].

It is worth mentioning that other infections can induce tHUS, such as: Salmonella tiphy, Campylobacter fetus jejuni, Yersinia pseudotuberculosis,Bacterioides, Neisseria meningitides, S pneumoniae Rocky Mountain spotted fever,microtatobiotes, Portillo virus, Cocksackie virus, ECHO virus, influenza, Epstein Barr, rotavirus, HIV, Epstein-Barr virus, Herpes simplex virus, fungal infections (including Aspergillus fumigates). Additionally, TMA can also be triggered by some vaccinations such as influenza triple-antigen vaccine ;Typhoid-paratyphoid A and B (TAB), vaccine and Polio vaccine[1].

Finally, SHU and MAT injury can be triggered by other diseases, as are the cases of: Collagen -vascular disorder (eg, sclerodermia, lupus, antiphospholipid antibody syndrome),primary glomerulopathies, cancer, malignant hypertension, drugs (clopidogrel, calcineurin inhibitors, antineoplastic drugs), transplants and pregnancy. These were considered condition amplifying complement but last HUS consensus named them as secondary HUS, reflecting a narrow boundary between a HUS and these conditions in some cases and circumstances. Thus, distinguishing between aHUS, tHUS, secondary HUS and thrombocytopenic thrombotic purpura (TTP) is essential in terms of prognosis and treatment.

Regarding aHUS, it has been documented the following poor prognostic factors:

- Non-Shiga - toxine -HUS
- Prolonged oliguria or anuria
- Severe hypertension (especially delayed onset of hypertension)
- Involvement of medium-sized arteries
- Severity of central nervous system (CNS) symptoms
- Persistent consumption of clotting factors
- Extensive glomerular involvement (>80%)

- Age older than 5 years

**Atypical haemolytic uraemic syndrome (aHUS)**

More than 50% of patients with aHUS require dialysis or have permanent kidney damage during the year following diagnosis[1,3]. This alteration may be caused by mutations or polymorphisms that decrease the activity of complement regulatory proteins or enhance the function of activating proteins. With more than 1,000 patients suffering from aHUS published in the literature, mutations have been detected in one or more complement proteins in 50% of them[7,8]. It has also been described 5-10% of autoantibodies against complement factor H (CFH) in aHUS[9, 10]. Its clinical beginning is usually abrupt, although in 20% of patients it may be progressive (weeks or months) with subclinical anemia, fluctuating thrombocytopenia and preserved renal function[2]. As it was mentioned above, its clinical picture is characterized by the triad of non-immune microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure[1]. High levels of lactate dehydrogenase (LDH), undetectable levels of haptoglobin and the presence of schistocytes confirm the presence of intravascular hemolysis[1]. Hematuria, proteinuria and / or acute renal failure (with or without oligoanuria) are usually observed. The presence of arterial hypertension, volume overload or vascular injury is also frequent[1].

STEC-HUS is usually a unique event, meanwhile aHUS is a chronic entity with worse prognosis. After a first episode of aHUS mortality is 10-15% and up to 50% of patients do not recover their renal function[10,11].

Even though, aHUS lesions predominantly affect the renal vessels, the diffuse nature of the TMA phenomenon can lead to the involvement of the microvasculature of other organs (brain, heart, intestines, pancreas and lungs), which explains the frequent occurrence of extrarenal symptoms[1,10]. The most frequent of them are neurological (48%), including irritability, drowsiness, confusion, convulsions, encephalopathy, stroke, hemiparesis, hemiplegia or coma[12,13]. Myocardial infarction has been described in up to 3% of patients with aHUS, and may be related to sudden death[12]. Cardiomyopathy, heart failure and peripheral ischemic vasculopathy have also been described, as well as diarrhea (30%) and other gastrointestinal symptoms (colitis, nausea and vomiting or abdominal pain). The variability of the symptoms makes difficult the differential diagnosis with other causes of TMA, and recurrences of post-renal transplant (RT) disease is around 50%, depending on the existing mutation. FH mutations are associated with an increased risk of recurrence or graft loss after TR (75-90%), and 40-80% in C3 and Factor I (FI)[15-20].

It has been recently reported that up to 25% of patients with STEC-HUS and 86% of patients with HUS secondary to pregnancy may present mutations in the complement system, and it may be considered in these cases that the underlying disease is really a aHUS[21].

Since there are patients on hemodialysis who have diagnosis of HUS, and many of them are enrolled in a waiting RT list, the pathophysiology of their HUS should be understand in terms of knowing prognosis, and planning prophylaxis for their future renal transplant.

**The complement system (CS)**

The CS is an essential part of innate immunity, with critical roles in response to pathogens and the removal of cells debris and immune complexes. Complement is activated through the classic, lectin and alternative pathways resulting in the formation of unstable biomolecular complexes called C3 convertases. C3 can hydrolyze, spontaneously into C3 (H2O) a molecule that mimics the C3 cleavage product C3b and confers upon the alternative pathway the ability to bypass a particular activator. It is always "on" at a low level. Under physiologic conditions this low level activation is controlled by complement regulatory proteins, both soluble and present on the surface of most eukaryotic cells[22].

Pathogens usually do not have complement regulators on their surfaces to inhibit this spontaneous activation. C3b molecules incorporation to surface -bound C3 convertases then generates C5 convertases, cleaving C5 and leading to formation of C5a (an anaphylotoxin) and C5b-9 (membrane attack complex MAC) setting up an inflammatory response and destroying the pathogens. Regulation of such alternative complement pathway activations in a complex process involving 2 soluble proteins, CFH y CFI and several membrane- bound proteins, membrane cofactor protein (MCP), thrombomodulin (THBD), complement receptor I (CRI), and decay accelerating factor (DAF)[22]. The activity of these molecules preserves complement homeostasis, endothelial cell activation and injury, as well as platelet activation, aggregation and inflammation. Many of these proteins are encoded by genes within a cluster known as RCA (regulator of complement activation) on human chromosome 1q32[22].

Analysis of hundreds of patients with a HUS through international collaborative studies has established that approximately 70% carry identifiable genetic abnormalities that alter the regulation of the alternative pathway. Theses mutations are heterozygous in approximately 90% of cases[23]. Most lead to loss of protein function, with the exception of those related to complement alterations which are identified in 15% of aHUS cases[24]. Mutations cannot be identified in 30% of aHUS cases. So not finding a mutation functionally characterized in the literature as pathogenic does not exclude dysregulation of the alternative pathway, nor prove that a genetic component is not involved. Incomplete penetrance must also be considered. Certain mutations particularly in MCP may be associated with milder disease and few relapses[25]. Acquired auto antibodies against CFH have been identified in some cases, with greater than 90%of such patients homozygous for a polymorphism deleting CFH R3 and /or CFH R1 genes[4, 25].

**STEPS FOR DIAGNOSIS OF A HUS**

First step is to determine the presence of laboratory criteria for microangiopathic hemolytic anemia: The initial laboratory assessment consist in finding the presence of the following elements (peripheral blood smears and urine spot) although not all of them are necessary to confirm diagnosis: Decreased hematocrit and hemoglobin and thrombocytopenia ; schistocytes on peripheral blood smears, elevated LDH, low haptoglobin, elevated indirect bilirrubin, elevated reticulocytes and low C3 level are the laboratory initial parameters to look for[4,21]:

- Hemoglobin concentrations may fall as low as 4-5 g / dl. Leukocytosis is a frequent sign (they may play a role in the pathogenesis of HUS, since they are mediators of endothelial injury).

- Platelets almost always fall in the first week to below 100,000 / mm3 but usually never lower than 30000 mm (different from TTP).

- The presence of hemolytic anemia is constant, with erythrocyte fragmentation (abnormal red blood cells, spherocytes and bizarre variety).

- Schistocytes may be infrequent on initial presentation as intact reticuloendothelial and splenic function is capable of clearing red cells with damaged membranes, despite the presence of other laboratory and clinical manifestations of TMA. The hemolysis intensity is highest in the first week, and then declines.

- LDH elevated 2 times the upper limit of normal range, is characteristic of TMA. At the beginning its serum augment is a consequence of both hemolysis and tissue ischemia, but when plasmapheresis treatment (PT) starts, LDH declines but does not normalize (different from PTT that normalizes LDH after PT.

- LDH isoenzyme analysis has shown that a substantial portion of LDH elevation in a TMA may be attributable to its release from tissue damaged as a result of microthrombosis- associated ischemia which in not corrected by PE in aHUS. This accounts due to the fact that in an acute TMA, LDH elevations may be not in proportion to the degree of red cells destruction with minimal changes in the indirect bilirrubin.

- Decreased or undetectable serum haptoglobin levels are classic for any hemolytic anemia evidencing a process of intravascular hemolysis. Haptoglobin is an acute -phase reactant considered positive reactant it means that the justification for its abnormal level due to inflammatory process must be explained by its elevation not due to its decreased level.

- The reticulocyte response is precocious and ranges from 1 to 20%.

- Coagulation studies show normal or high activity of factor VIII, factor V, fibrinogen, fibrin monomers and fibrinogen degradation products. One-third of patients have partial thromboplastin time shortening, while antithrombin III is normal but may be low.

- C3 consumption or low level detection was first described by Cameron in 1973. Determining/measurement of the circulating complement levels as low C3 level with normal or elevated C4 level is classically seen when there is activation of the alternative complement pathway seen in aHUS, but it is not so frequently observed.
  Serum C3 is normal in up to 80% of aHUS patients. Complement can also be activated in TTP, leading to elevated levels of C5a and C5b-9, as in a HUS. Measurement of C5b-9 in urine or properly processed plasma may help identify a TMA but not distinguish a primary TMA from a related complement activated condition (secondary TMA) nor TTP from aHUS[26]

- Urine spot: in approximately 20% of initial aHUS there is scarce creatinine alteration but haematuria and microalbuminuria are usually present.

- It should look for proteinuria and hematuria : all patients present microhematuria, and may present all types of urinary cylinders, with variable range proteinuria. These findings are not necessarily found in TTP.

**CONCLUSION:** aHUS is an ultrarare disease that share with other clinical entities anatomopathological features (TMA) and laboratory abnormalities.

aHUS appears in the presence of mutation or polymorphisms of proteins that regulate the alternative pathway of complement, mainly CFH y CFI and several membrane-bound proteins, membrane cofactor protein (MCP), thrombomodulin (THBD). The certain diagnosis for aHUS includes genetic tests that confirm mutations linked to the syndrome. However it is widely known that only approximately 50% to 60% of available genetic tests are diagnostic and that racial differences also contribute to incomplete gene files. So, to establish the more accurate differential diagnosis between TTP, tHUS, and secondary causes of TMA is essential to come to an adecuate diagnosis that let the specific treatment to be performed even in the absence of genetic confirmation. First diagnosis steps for aHUS are shared with the others causes of HUS but slight differences may contribute to elucidate the differential diagnosis between them.

**REFERENCES**

1.- Campistol JM, Arias M, Ariceta G, Blasco M, Espinosa L, Espinosa M, Grinyó JM, Macía M, Mendizábal S, Praga M, Román E, Torra R, Valdés F, Vilalta R, Rodríguez de Córdoba S. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia. 2015;35(5):421-447.

2.- Brunelli SM, Claxton A, Mehta S, Anum EA. Consequences of hemolytic uremic syndrome among hemodialysis patients. J Nephrol. 2015;28(3):361-367.

3.- Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011. 6:60.10.1186/1750-1172-6-60

4.- Laurence J, Haller H, Mannucci PM, Nangaku M, Praga M, Rodriguez de Cordoba S. Atypical hemolytic uremic syndrome (aHUS): essential aspects of an accurate diagnosis. Clin Adv, Hematol Oncol. 2016 Nov;14 Suppl 11(11):2-15.

5.- Caprioli J, Bettinaglio P, Zipfel PF, Amadei B, Daina E, Gamba S, Skerka C, Marziliano N, Remuzzi G, Noris M; Itaslian Registry of Familial and Recurrent HUS/TTP. The molecular basis of familial hemolytic uremic syndrome: mutation analysis of factor H gene reveals a hot spot in short consensus repeat 20. J Am Soc Nephrol. 2001; 12(2):297-307.

6.- Fremeaux-Bacchi V, Kemp EJ, Goodship JA, Dragon-Durey MA, Strain L, Loirat C, Deng HW, Goodship TH.The development of atypical haemolytic-uraemic syndrome is influenced by susceptibility factors in factor H and membrane cofactor protein: evidence from two independent cohorts. J Med Genet. 2005;42(11):852-856.

7.- Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C; French Society of Pediatric Nephrology. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 2007;18(8):2392-2400.

8.- Maga TK, Nishimura CJ, Weaver AE, Frees KL, Smith RJ. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. Hum Mutat 2010;31(6):E1445-60.

9.- Boyer O, Balzamo E, Charbit M, Biebuyck-Gougé N, Salomon R, Dragon-Durey MA, Frémeaux-Bacchi V, Niaudet P.Pulse cyclophosphamide therapy and clinical remission in atypical hemolytic uremic syndrome with anti-complement factor H autoantibodies. Am J Kidney Dis 2010;55(5):923-927.

10.- Lionet A, Provôt F, Glowacki F, Frémeaux-Bacchi V, Hazzan M. A case of adult atypical haemolytic uraemic syndrome related to anti-factor H autoantibodies successfully treated by plasma exchange, corticosteroids and rituximab. NDT Plus 2009;2:458.

11.- Noris M, Mescia F, Remuzzi G. Atypical Hemolytic - uremic. N Engl J Med. 2009; 361 (17):1676-1687.

12.- Licht C, Pluthero FG, Li L, Christensen H, Habbig S, Hoppe B, Geary DF, Zipfel PF, Kahr WH.Platelet- associated complement factor H in healthy persons and patients with atypical HUS.Blood 2009; 114(20):4538-4545.

13.- Riedl M, Fakhouri F, Le Quintrec M, Noone DG, Jungraithmayr TC, Fremeaux-Bacchi V, Licht C. Author informationSpectrum of complement-mediated thrombotic microangiopathies: pathogenetic insights identifying novel treatment approaches. Semin Thromb Hemost.2014;40(4):444-6410.

14.- Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. Nat Rev Nephrol. 2014 Mar;10(3):174-180

15.- Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C; French Society of Pediatric Nephrology. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007;18(8):2392-2400.

16.- Caprioli J, Castelletti F, Bucchioni S, Bettinaglio P, Bresin E, Pianetti G, Gamba S, Brioschi S, Daina E, Remuzzi G, Noris M; International Registry of

Recurrent and Familial HUS/TTP. Complement factor H mutations and gene polymorphisms in haemolytic uraemic syndrome: the C-257T, the A2089G and the G2881T polymorphisms are strongly associated with the disease. Hum Mol Genet 2003;12(24):3385-3395.

17.- Esparza-Gordillo J, Jorge EG, Garrido CA, Carreras L, López-Trascasa M, Sánchez-Corral P, de Córdoba SR. Insights into hemolytic uremic syndrome: Segregation of three independent predisposition factors in a large, multiple affected pedigree. Mol Immunol 2006;43(11):1769-1775.

18.- Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, Daina E, Fenili C, Castelletti F, Sorosina A, Piras R, Donadelli R, Maranta R, van der Meer I, Conway EM, Zipfel PF, Goodship TH, Remuzzi G. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 2010;5(10):1844-1859

19.- Loirat C, Noris M, Fremeaux-Bacchi V. Complement and the atypical hemolytic uremic syndrome in children. Pediatr Nephrol 2008;23(11):1957-1972

20.- Dragon-Durey MA, Sethi SK, Bagga A, Blanc C, Blouin J, Ranchin B, André JL, Takagi N, Cheong HI, Hari P, Le Quintrec M, Niaudet P, Loirat C, Fridman WH, Frémeaux-Bacchi V. Clinical features of anti-factor H autoantibodyassociated hemolytic uremic syndrome. J Am Soc Nephrol. 2010;21(12):2180-2187.

21.- Bresin E, Daina E, Noris M, Castelletti F, Stefanov R, Hill P, Goodship TH, Remuzzi G. Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol 2006;1(1):88-89.

22.- Rodriguez de Cordoba S, Esparza- Gordillo J, Goicochea de Jorge E, Lopez-Trascasa M,Sanchez Corral P. The human complement factor H: functional roles, genetic variations, and disease association. Mol Immunol. 2004;41(4)355-367.

23.- Rodriguez de Cordoba S,Hidalgo MS , Pinto S, Tortajada A. Genetic of atypical hemolytic uremic syndrome (aHUS). Sem Thromb Hemost.2014; 41(4): 422-430.

24.- Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S, Niaudet P, Deschênes G, Lebranchu Y, Zuber J, Loirat C. Genetic and outcome of atypical hemolytic uremic syndrome a nation wide French series comparing children and adults. Clin J Am Soc Nephrol.2013; 8 (4):554-562.

25.- Skerka C, Jozsi M, Zipfel PF, Dragon Durey M-A, Fremeaux Bacchi V.Autoantibodies in haemolytic uremic syndrome (HUS).Thromb Haemost.2009; 101(2): 227-232.

**CORRESPONDENCE:**

Dra. Rita Marcela Fortunato
Subjefa de la Unidad Renal del Hospital Universitario Fundación Favaloro.
Buenos Aires.
Argentina
Email: rfortuna @ ffavaloro

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**Comment of the reviewer Carlos G. Musso, MD. PhD.** Nephrology Division. Hospital Italiano de Buenos Aires, Argentina.

Monoclonal gammopathy of renal significance (MGRS) is a recently described hemato-nephrological meta-entity characterized by renal damage mediated by monoclonal immunoglobulin and/or cytokines secreted by small clone lymphoproliferative disorders.

It has been documented that MGRS is one of the atypical hemolytic uremic syndrome inducing conditions, being its potential pathophysiological mechanisms: the MGRS production of autoantibodies or humoral factors which could alter the patients` complement system activity.

**References**:
1.- Ciocchini M, Arbelbide J, Musso CG. Monoclonal gammopathy of renal significance (MGRS): thecharacteristics and significance of a new meta-entity. Int Urol Nephrol. 2017 Dec;49(12):2171-2175.
2.- Ciocchini M, Musso CG. What is the place of POEMS syndrome in the current classification of monoclonal gammopathies of renal significance? Int Urol Nephrol. 2017 Nov 13. doi: 10.1007/s11255-017-1739-z.

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**Comment of the reviewer Susana Gabriela Pérez MD.** Especialista en Nefrología. Posgrado de Efectividad Clínica, Analista de Datos Médicos en Diaverum. Argentina.

Atypical hemolytic uremic syndrome (aHUS) occurs in 10% of the cases of hemolytic uremic syndrome (HUS), in the remaining 90% the typical form is presented. aHUS is a rare disease, with a poor prognosis since most patients have recurrences and more than 50% develop end-stage renal failure (ESRD). Several studies have been published stating that the majority of patients with aHUS have a genetic component, associated with mutations and polymorphisms in genes that encode proteins of the complement system (for example, mutations in factor H identified in these patients that decrease the protection of cell surfaces from accidental damage caused by complement activation). In these patients genetic and environmental factors are associated in the development of the disease. However, in 5-10% of patients with HUS, the mutation was not identified and instead there were antifactor H autoantibodies with consequences similar to those of mutations in factor H. Although the meaning of these antibodies in the pathogenesis of HUS is not fully established,

its association with the onset or recurrence of the disease indicates a causal relationship with it.

As key concepts of the etiology of this form of aHUS, we can summarize two: on the one hand, more than 50% of patients have mutations in complement genes (factor H), while in those that do not, autoantibodies have been identified anti factor H. The consequence in both cases is the injury produced by the complement in the endothelium of the renal microvasculature.

**References**

1.- S. Rodríguez De Córdoba, T. Montes, Síndrome hemolítico urémico atípico. Nefrología Suplemento Extraordinario 2011;2:58-65.
2.- Caprioli J, Bettinaglio P, Zipfel PF, et al. The molecular basis of familial hemolytic uremic syndrome: mutation analysis of factor H gene reveals a hot spot in short consensus repeat 20. J Am Soc Nephrol 2001;12:297-307.
3.- Pérez-Caballero D, González-Rubio C, Gallardo ME, et al. Clustering of missense mutations in the C-terminal region of factor H in atypical hemolytic uremic syndrome. Am J Hum Genet 2001;68:478-84.