ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 12, pp.9120-9123, December, 2019

DOI: https://doi.org/10.24941/ijcr.37435.12.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

ATYPICAL HEMOLYTIC UREMIC SYNDROME IN CHILDREN

[1]Lazrak, F.Z., [1]Aourarh, S., [1]Jahdaoui, A., [1]Rahali, F.Z., [1]Sayagh, S., [2]Ait Ameur, M. and [2]Chakour, M.

[1]Laboratory of Hematology of University Hospital Mohammed VI - Marrakech
[2]Laboratory of Hematology Military Hospital Avicenna - Marrakech

ARTICLE INFO

Article History:
Received 14th September, 2019
Received in revised form
28th October, 2019
Accepted 29th November, 2019
Published online 31st December, 2019

Key Words:
Atypical Hemolytic Uremic Syndrome-children-Thrombotic Microangiopathy-C3- schizocytes-blood Smear.

ABSTRACT

Hemolytic Uremic Syndrome (HUS) is one of a group of disorders grouped together as thrombotic microangiopathy (TMA) and characterized by the association of mechanical haemolytic anemia, peripheral thrombocytopenia, and failure of organs of variable severity (1). Atypical HUS with a different clinical presentation and evolution, the onset may be misleading and as typical HUS manifest as diarrhea. Atypical HUS represents only 10% of HUS cases in children (3). Although some causes can be identified, the etiology of atypical HUS often remains unknown (4). Atypical HUS occurs at all ages. The clinical presentation and evolution are different from those of postdiarrheal HUS. Prodromes such as vomiting, fever, and upper respiratory infection are inconsistent. Atypical HUS often has an insidious onset and evolves by pushing or progressively a single outfit. A neurological impairment can be observed. A high proportion of patients maintain more or less severe renal insufficiency and high blood pressure. Nevertheless, some children have a less severe form and a favorable prognosis (2). We report a rare pediatric case of atypical HUS without schizocytes on a blood smear with a picture of haemophagocytosis associated with an infant aged 23 months.

Citation: Lazrak, F.Z., Aourarh, S., Jahdaoui, A., Rahali, F.Z., Sayagh, S., Ait Ameur, M. and Chakour, M. **2019.** "Atypical Hemolytic Uremic Syndrome in children", *International Journal of Current Research*, 11, (12), 9120-9123.

INTRODUCTION

Hemolytic Uremic Syndrome (HUS) is one of a group of disorders grouped together as thrombotic microangiopathy (TMA) and characterized by the association of mechanical haemolytic anemia, peripheral thrombocytopenia, and failure of organs of variable severity (Coppo, 2005). It is the leading cause of acute renal failure in children under three years of age. In its typical form, HUS occurs during the summer period after an episode of diarrhea, often bloody (Niaudet, 2008). Atypical HUS with a different clinical presentation and evolution, the onset may be misleading and as typical HUS manifest as diarrhea. Atypical HUS represents only 10% of HUS cases in children (Fitzpatrick, 1993). Although some causes can be identified, the etiology of atypical HUS often remains unknown (Neuhaus, 1997). Atypical HUS occurs at all ages. The clinical presentation and evolution are different from those of postdiarrheal HUS. Prodromes such as vomiting, fever, and upper respiratory infection are inconsistent. Atypical HUS often has an insidious onset and evolves by pushing or progressively a single outfit.

****Corresponding author:*** **Lazrak, F.Z.,**
Laboratory of Hematology of University Hospital Mohammed VI – Marrakech.

A neurological impairment can be observed. A high proportion of patients maintain more or less severe renal insufficiency and high blood pressure. Nevertheless, some children have a less severe form and a favorable prognosis (Niaudet, 2008). We report a rare pediatric case of atypical HUS without schizocytes on a blood smear with a picture of haemophagocytosis associated with an infant aged 23 months.

Observation: This 3-month-old boy had been hospitalized for kidney failure. He came from a non-consanguineous marriage, a well-conducted term pregnancy without incident with normal psychomotor and normal weight development. Three weeks before admission, he had episodes of fluid diarrhea at 5 to 6 stools per day complicated 5 days later by dehydration, convulsion and anuria that lasted for 4 days, all associated to fever at 38C. Clinical examination revealed puffiness of the face with palpebral edema, with crusty squamous skin lesions suggestive of ichthyosis associated with intense cutaneous mucosa with discolored conjunctiva. The biological assessment at entry showed hypochromic microcytic anemia (hypochromic hemoglobin = 5.4 g / dl) (mean corpuscular volume (MCV) = 78.9 m3, mean hemoglobin concentration (MCHC) = 30.2%) and thrombocytopenia. at 7000 / mm3. The blood smear showed the presence of haemophagocytosis of

neutrophils vacuolated, poikilocytosis of Red blood cell with ,the presence of Jolybody without schizocytes. Creatinine was 13.2 mg / L and urea was 1.91 g / L. Stool culture and PCR were negative. cytobacterioligical urine exam did not isolate germ and LP was sterile. The gastrointestinal syndromic diagnosis was negative. The haemolysis report showed total bilirubin at 1.5 mg / L and lactate dehydrogenase at 1102 U / L. The liver and hemostasis balance were unremarkable with a parathyroid hormone elevated to 128.2 Pg / ml. Similarly, transfontanellar ultrasound and cerebral CT were normal. The diagnosis of atypical HUS had been suspected indicating complement dosage.

DISCUSSION

HUS is characterized by the association of mechanical haemolytic anemia, peripheral thrombocytopenia and acute renal failure secondary to microangiopathy (TMA)(Marie-Agnès, 2006). These renal or extra-renal histopathological lesions are characterized by a thickening of the walls of glomerular capillaries or arterioles with presence of platelet microaggregates (Noris, 2005). They are due to an endothelial aggression resulting in endothelial cell activation or injury. Schematically, four phases intervene in the occurrence of TMA lesions: vascular endothelial lesion, platelet adhesion and aggregation at the origin of Microplate thrombi, decreased fibrinolytic activity and finally hemolysis with formation of schizocytes. There are two main groups of HUS in children; so-called typical or post-diarrheal epidemic HUS and atypical HUS. The typical form is the most common (90-95%) and one of the leading causes of acute renal failure in children <3 years of age (Loirat, 2001). Postdiarrheal HUS is associated with an episode of Escherichia coli (E. coli) or Shigelladysenteriae colitis that occurs in the ten days preceding the HUS. The bacterial strain of E. coli O157: H7 is most frequently isolated, but others have also been described. These bacteria release toxins called Shiga-toxins (for S. dysenteriae) and Shiga-like toxins (for E. coli), given their structural analogy. The bacteria is contracted during the consumption of dairy products, meat, sausages, or by ingestion of dirty water. The toxins released into the lumen of the digestive tract pass through the brush border and are transported by the neutrophils to the endothelial cells of the capillaries of the renal microcirculation. These toxins cause the activation or death by apoptosis of endothelial cells, and the expression of tissue factor on the surface of these cells, which leads to the formation of microthrombi in the renal capillaries (Coppo, 2005), which leads to hemolysis.

Clinically, typical HUS is characterized by a prodromal phase marked by abdominal pain, vomiting and often glaring diarrhea (Loirat, 2001). HUS then occurs abruptly after an interval between 1 and 10 days, associating anemia, thrombocytopenia and renal failure (Andreoli, 2002). Anemia is a mechanical haemolytic type characterized by the presence of schizocytes. As has been demonstrated in several studies, the absence of schizocytes does not eliminate the diagnosis of TMA (Daram, 2005) and a thorough examination of the smear should be performed before concluding the result as a false negative. Peripheral thrombocytopenia is the first biological sign (Bahloul, 2006) associated with excessive consumption (Coppo, 2005). The diagnosis of E. coli O157: H7 infection can be made by stool culture on MacConkey medium containing sorbitol. Stool culture is only positive for a few days after the onset of diarrhea. The search for VT1 genes in stools can be performed by PCR and IgM antibodies can be detected against the lipopolysaccharide of VT1 (Niaudet, 2008). Acute renal failure with oligoanuria is observed in half of the cases (Niaudet, 2008). In other cases, there is hematuria, proteinuria and moderate impairment of renal function (Niaudet, 2008). Given the severity of the clinical-laboratory picture that occurred following a diarrheal episode in the child of our observation and the absence of verotoxigenic secreting organisms in all the diagnostic techniques mentioned above, the diagnosis was oriented towards atypical HUS. Atypical HUS represent only 5 to 10% of HUS cases (Loirat, 2012). Their clinical presentation is different from post-diarrheal forms and they frequently evolve into chronic renal failure. In 60 to 80% of cases they follow a gastroenteritis or an infection of the upper respiratory tract. The frequency of an episode of diarrhea triggering atypical HUS shows how fragile the prodromal diarrhea criterion is in differentiating the two types of HUS (Loirat, 2012).

Atypical HUS can occur at any age; from birth or the first weeks of life to adulthood (Loirat, 2005). Relapses are frequent with periods of remission more or less long. These atypical forms may be sporadic or familial with mostly recessive inheritance (Andreoli, 2002). They group together heterogeneous clinico-biological entities constituting subgroups of atypical HUS from different etiopathogenic mechanisms (Loirat, 2005). Histological involvement often consists of arteriolar TMA (Niaudet, 2008). Clinically, fever is present in 60 to 90% of cases. Neurological impairment is characterized by its sudden onset and fugacity. It can manifest as a picture of convulsions, headaches ,consciousness disordersranging from confusion to coma. Sensory or motor deficit can also be observed with MRI angiography (Loirat, 2012; Caron, 2006). In our observation, the neurological involvement was limited to a convulsion and the brain scan was normal. The biological assessment reveals a hemolyticanemia often deep with presence of schizocytes with the blood smear in favor of its mechanical origin. The search for schizocytes must be repeated. Indeed, they may appear delayed in relation to hemolysis (Caron, 2006). In our observation, the search for schizocytes was negative with presence of hemophagocytosis picture, according to data from the literature, the finding of isolated images of hemophagocytosis does not appear sufficient to bring the diagnosis of HUS, a hemophagocytic mechanism could nevertheless contribute to the development of thrombocytopenia during sepsis (François, 1995). Atypical HUS may be secondary to a deficiency of factor H or I deficiency, ADAMTS 13 deficiency, or vitamin B12 deficiency.

Atypical SHU and complement: Mutations of several genes encoding complement proteins, particularly alternative regulatory proteins, have been found in atypical forms of HUS. Such abnormalities would be responsible for approximately 50% of atypical HUS (Niaudet, 2008). The Activation of the alternate pathway of the complement results in the formation of a C3 convertase that cleaves C3 and generates C3b. the C3b, on the surface of a so-called activating substance, binds to factor B to form C3b, the Factor B is cleaved by factor D , resulting in the formation of C3 convertase, C3b, Bb which activates the amplification loop and allows the formation of the membrane attack complex. Circulating regulatory proteins of the alternative pathway exist: factor H (CFH) and factor I (CFI). Factor H binding to C3b allows Factor I to cleave C3b to C3bi.

It therefore inhibits the formation of alternating C3 convertase and promotes its degradation (Niaudet, 2008). The CFH, synthesized by the liver, is encoded by a gene located on chromosome 1, in a locus called regulators of complement activation (RCA) including genes encoding different complement regulatory proteins. Other cell surface proteins, such as the membrane cofactor protein (MCP or CD46), complement receptor 1 (CR1 or CD35) or decay accelerating factor (DAF or CD55) also have a role of regulating the alternate pathway.

Atypical SHU and Willebrand factor protease deficiency

The von Willebrand factor is a glycoprotein that transports circulating factor VIII and allows adhesion and aggregation of platelets. Broad multimers of von Willebrand factor are more effective for platelet adhesion and aggregation than dimers. These multimers from endothelial cells and platelets do not pass into the circulation because they are cleaved by a specific protease, a metalloprotease synthesized by the liver. This protease is the thirteenth of the ADAMTS family. The gene encoding this protease is located on chromosome 19. Many cases of thrombotic thrombocytopenic purpura in adults are related to a von Willebrand factor protease deficiency (Furlan, 1998). This deficiency can be transmitted according to the autosomal recessive or acquired mode in connection with an acquired auto-antibody which neutralizes the activity of the protease (Kokame, 2002). A few cases of atypical HUS in children have been reported in association with von Willebrand factor protease deficiency secondary to mutations in the ADAMTS 13 gene (Veyradier, 2003). Most cases occur from birth with hemolyticanemia and thrombocytopenia. Renal involvement appears later with a gradual evolution. A later start is possible. A deficiency of Willebrand factor protease activity has also been reported in an adult with a factor H mutation with severe clinical manifestations of thrombotic thrombocytopenic purpura and renal failure (Noris, 2005).

HUS associated with congenital deficiency of vitamin B12 metabolism: Vitamin B12 or cobalamin is the coenzyme of methionine synthase that converts homocysteine to methionine. It is also the coenzyme of methylmalonyl CoA mutase which converts methylmalonyl CoA to succinyl CoA. Children with a cobalamin C mutation have a functional deficiency of methylmalonyl CoA mutase and methionine synthase responsible for methylmalonicacidemia with homocystinuria. About a quarter of cases are accompanied by HUS (Kind, 2002). The first symptoms appear in the neonatal period with anorexia, vomiting, hypotonia, convulsions and lethargy. The first signs of HUS occur between the end of the first month and the third month. Hemolyticanemia with schizocytes is severe and is accompanied by macrocytosis. Thrombocytopenia is common. Renal involvement is marked by hematuria, proteinuria and renal failure. Chromatography of amino and organic acids shows a considerable increase in homocysteine and a decrease in methionine in plasma and a high urinary excretion of homocysteine and methylmalonic acid. Treatment should be started early (hydroxycobalamin, folinic acid and betaine). The vital and neurological prognosis depends on the precocity of the treatment (Niaudet, 2000).

Autosomal recessive HUS of unknown etiology: Autosomal recessive HUS without identified cause is seen primarily in children with early onset of neonatal onset (Kaplan, 1992). The disease usually starts at the same age among siblings. The beginning is often progressive and relapses are frequent. The disease most often progresses to end-stage renal failure.

Autosomal dominant SHU of unknown etiology: This form of SHU is less frequent than the previous one. The onset of the disease occurs at different ages among members of the same family. The disease can begin in childhood. The prognosis is most often unfavorable (Kaplan, 1992; Kaplan, 2000).

REFERENCES

Andreoli S, Trachtman H, Acheson D, *et al*., 2002. Hemolytic-uremic syndrome: epidemiology, physiopathology and therapy. *Pediatr Nephrol.,* 17:293–8.

Bahloul M., Ben Hamida C., Dammak H. 2006. Les microangiopathiesthrombotiquesen reanimation. *Ann Fr Anesth Reanim*., 25:820–7.

Caron C. 2006. Prote´ase de clivage du facteur Willebrand (ADAMTS13) et purpura thrombotique thrombocytope´nique. Rev Fr Laboratoires378:21–8.

Coppo P, Vernant JP, Veyradier A. *et al*., 2005. Purpura thrombotique et autres syndromes de microangiopathie thrombotique. EMC Hematol, 2:14–34

Coppo P., Veyradier A. 2005. Microangiopathies thrombotiques: physiopathologie, diagnostic et traitement. Reanimation., 14: 594–603.

Daram SR, Philipneri M, Puri N, *et al*., 2005. Thrombotic thrombocytopenic purpura without schistocytes on the peripheral blood smear. *South Med J.,* 98:392–5.

Fitzpatrick MM, Walters MD, Trompeter RS, Dillon MJ, Barratt TM. 1993. Atypical (non-diarrhea-associated) hemolytic-uremic syndrome in childhood. *J Pediatr.,* 122:532—7.

François, B., Trimoreau, F., Vignon, P., Verger, G., &Gastinne, H. 1995. Syndrome hémophagocytaire réactionnel : une cause probablement sous-estimée de thrombopénie en réanimation. Annales Françaises d'Anesthésie et de Réanimation, 14(6), 514–516.

Frémeaux-Bacchi, V., Fakhouri, F., Roumenina, L., Dragon–Durey, M.-A., &Loirat, C. 2011. Syndrome hémolytique et urémique lié à des anomalies du complément. La Revue de Médecine Interne, 32(4), 232–240.

Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B. *et al*., 1998. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med*., 339:1578—84.

Kaplan B., Leonard M. 2000. Autosomal dominant haemolytic-uremic syndrome: variable phenotypes and transplant results. *Pediatr Nephrol*.,14:464—8

Kaplan BS, Kaplan P. 1992. Hemolytic-uremic syndrome in families. In: Kaplan BS, Trompeter R, Moake J, editors. Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura. New York: Dekker; p. 213—25

Kind T, Levy J, Lee M, Kaicker S, Nicholson JF, Kane SA. 2002. Cobalamin C disease presenting as hemolytic-uremic syndrome in the neonatal period. *J Pediatr Hematol Oncol.,* 24: 327—9.

Kokame K, Matsumoto M, Soejima K, Yagi H, Ishizashi H, Funato M, *et al*. Mutations and common polymorphisms in ADAMTS 13 gene responsible for von Willebrand factor-cleaving protease activity. Proc Natl AcadSci USA 2002;99:11902—7.

Loirat C. 2001. Syndrome hémolytique et urémique typique post diarrhée : aspects cliniques. Arch Pediatr 8(Suppl. 4):776–84.

Loirat C. 2012. Syndrome hémolytique et urémique chez l'enfant. *EMC Pediatr Mal Infect*., 7:1–14.

Loirat C., Sellier AL., Frémeaux-Bacchi V. *et al*., 2005. Syndromes hémolytiques et urémiques et purpuras thrombotiques thrombocytopéniques héréditaires : progrès récents. Journ Paris Pediatr, 97–110 (Flammarion Me´decine-Sciences).

Marie-Agnès Dragon-Durey, 2006. Véronique Fremeaux-Bacchi. Déficits en protéines du complément en pathologie humaine. Presse Med. 2006; 35: 861-70 ©, Masson, Paris

Neuhaus TJ, Calonder S, Leumann EP. 1997. Heterogeneity of atypical haemolytic-uremic syndromes.*Arch Dis Child.,* 76:518—21.

Niaudet P, Gagnadoux M, Broyer M, *et al*., 2000. Hemolytic-uremic syndrome: hereditary forms and forms associated with hereditary diseases. *Adv Nephrol Necker Hosp*., 30:261—80.

Niaudet, P. 2008. Syndrome hémolytique et urémique chez l'enfant. Néphrologie & Thérapeutique, 4(1), 34–40.

Noris M, Bucchioni S, Galbusera M. 2005. Complement factor H mutation. *J Am Soc Nephrol*., 16:1177

Noris M, Remuzzi G. 2005. Hemolyticuremic syndrome. Am J Soc Nephrol16:1035–50.

Veyradier A., Obert B., Haddad E., Cloarec S., Nivet H., Foulard M. *et al*., 2003. Severe deficiency of the specific von Willebrandfactorcleaving protease (ADAMTS 13) activity in a subgroup of children with atypical haemolytic-uremic syndrome. *J Pediatr*., 142: 310—7.

****