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CASE REPORT

HEMOLYTIC-UREMIC SYNDROME ASSOCIATED WITH ACUTE DIARRHEIC DISEASE IN CHILDREN (CASE REPORT)

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Abstract. The Haemolytic-Uremic Syndrome (HUS) is the most frequent cause of renal failure in small children. This disease is often preceded by an episode of acute gastroenterocolitis caused by an enterohemorrhagic strain of Escherichia coli (0157:H7); the syndrome has been rarely associated with other bacterial or viral infections. HUS is more common in children younger than 4-5 years of age. The diagnosis is confirmed by microangiopathic haemolytic anemia, thrombocytopenia, and acute renal failure. A more careful medical evaluation of the hematological and renal manifestations, together with early and repeated hemodialysis, give the best chance of recovery, even in the acute phase of the diseases.
Keywords: haemolytic-uremic syndrome, Escherichia coli, therapy, children

Definition

The Haemolytic-Uremic Syndrome (HUS) was first described in 1955 by Gasser et al., and it is characterized by a triad of microangiopathic haemolytic anemia, thrombocytopenia and acute renal failure. It is the most common cause of renal failure in children. Despite similar clinical features and therapeutic approaches, HUS and *thrombotic thrombocytopenic purpura* are two separate entities.

Ninety percent of HUS are associated with acute diarrheic disease due to enterohemorrhagic O157:H7 *E coli* infections; this specific strain produces an enterotoxin that leads to endothelial cell damage, renal microvascular thrombosis, glomerular and tubular epithelial cell damage, and severe acute tubular necrosis.

Etiology

E coli serotype O157:H7 has been associated with more than 80% of all infections leading to HUS. This syndrome often occurs within 7-10 days after an episode of severe acute gastroenterocolitis. Usually, *E coli* O157:H7 cannot be identified in human intestinal flora, but it can be found in 1% of healthy beef cattle. Thus, meat may be contaminated during processing.

The most common form of transmission to children is the intake of undercooked meat containing viable bacteria. Other routes of transmission are: intake of non-pasteurized milk, unwashed fruit, juices, and contact with water without chlorine. Person-to-person transmission has been reported in day care or long-term care units, through contaminated toys and dirty hands. Outbreaks of infection have occurred following the use of swimming-pools with contaminated water.

The bacteria develop a toxin called **verotoxin**, which is responsible for the clinical symptoms of the disease. This toxin is also called **Shiga-like toxin**, due to its similarities to the Shiga toxin, pro-

duced by strains of Type I *Shigella dysenteriae*. The shiga-like toxin affects endothelial cells and causes intravascular thrombogenesis. After entering the circulatory system via the gastrointestinal mucosa, the toxin settles mostly in the kidneys, inhibiting the protein synthesis and leading eventually to cell necrosis or apoptosis. Endothelial cell damage subsequently causes renal microvascular thrombosis by enhancing the activation of the blood coagulation cascade. The platelet aggregation results in a consumptive thrombocytopenia. The microangiopathic haemolytic anemia is caused by the mechanical damage inflicted to the red blood cells circulating in the partially occluded microcirculation.

Other causes of HUS include:

- Other bacteria, such as: *Shigella, Salmonella, Campylobacter, Streptococcus pneumoniae, Bartonella,* and *Clostridium difficile*. The infection with *Streptococcus pneumoniae* is the second most frequent cause of HUS (20% of all cases), but the most common illness caused by *S. pneumoniae* is the acute lobar pneumonia.
- Some viral infections: Coxsackie virus, ECHO virus, Influenza virus, Varicella zoster virus, HIV, Epstein-Barr virus
- Drug-associated HUS: anti-cancer drugs (mitomycin, cisplatin, bleomycin, gemcitabine), immunotherapeutic drugs (cyclosporine, tacrolimus, interferon, quinidine), anti-platelet agents (ticlopidine, clopidogrel), oral contraceptives
- Underlying medical conditions such as: bone marrow transplant, systemic lupus erythematosus, antiphospholipid syndrome, pregnancy

Atypical HUS includes cases which are not associated with other entities. These are genetically determined and occur without prodromal diarrhoea.

Epidemiology

HUS typically occurs in infants and children, particularly those 6 months to 8 years old. It is endemic in Argentina, southern Africa and western United States. HUS is neither sex nor race oriented. Its incidence peaks during the warm periods, when the frequency of diarrheic diseases is higher, especially the infection with enterohemorrhagic *E. coli*. The overall incidence of HUS is estimated to almost 2.1 cases per 100,000 persons. We provide medical care for HUS patients in Romania; however, its incidence is currently unknown.

Pathogenesis

Although there are a number of hypotheses regarding the etiology of HUS, the current understanding of the basis of this disease is limited and still remains in the area of assumptions. The infectious etiology hypothesis has been suggested by the fact that the HUS is often preceded by an acute episode of digestive or respiratory infection.

Another concept related to the HUS etiopathogenesis suggests that HUS is a vasculitis affecting mainly the kidneys, the colon and the central nervous system.

Another pathogenic hypothesis suggests the possibility of an abnormal immune response to an infection (HUS related to *Streptococcus pneumonia*), which may lead to circulating immune complex formation; these remain in the blood circulation and are filtered by the kidneys, producing endothelial cell damage. Microangiopathic haemolytic anaemia is caused by the mechanical damage of the red blood cells circulating through partially occluded microcirculation. Thrombocytopenia is due to both *intra-renal* platelet *adhesion* and platelet damage. The pathogenesis of renal failure in HUS includes the binding of *E. coli* verotoxin to the glomerular mesangial cells, with subsequent effects on the renal function. This specific binding to the mesangial cells membrane has been demonstrated by immune fluorescence microscopy.

Histopathology

HUS causes glomerular damage such as: endothelial thickening with capillary lumen occlusion, endothelial cells with fused podocytes, thrombi and fibrin accumulation in renal arterioles and capillaries, which may result in cortical necrosis. The renal glomerular injury progresses to partial or total sclerosis.

Clinical manifestations

Usually HUS starts as an acute gastroenteritis, followed 4-10 days later by a sudden onset of symptoms such as pallor (worsened by haemolytic anemia), alteration of the clinical status, irritability, asthenia, lethargy and oliguria.

Physical examination reveals acute dehydration syndrome, petechiae, oedema, hepatosplenomegaly, oliguria or anuria and hypertension. Neurological symptoms may be observed and they include irritability, seizures or altered mental status.

Gastrointestinal bleeding and peritonitis were rarely described.

Cardiac damage may be severe and may consist of congestive heart failure and cardiac arrhythmias.

Micro-infarctions in the pancreas may cause pancreatitis or, rarely, insulin-dependent diabetes mellitus.

Ocular involvement may lead to retinal or vitreous haemorrhagings.

Laboratory tests

Haematological changes consist of haemolytic anaemia (with negative Coombs test); peripheral blood smear shows specific morphological aspects of microangiopathic anaemia (fragmented erythrocytes, schistocytes). Haemoglobin is less than 9g/dl, the reticulocyte count is moderately increased (a sign of acute haemolysis) and the platelet count is decreased (various degrees of thrombocytopenia: 20.000-100.000/cmm). Moderate leukocytosis may be present, but rarely more than 20.000/cmm.

Prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen are within normal ranges.

Elevation of lactate dehydrogenise (LDH) and indirect bilirubin levels (2-3mg/dL) show intravascular haemolysis.

The nitrogen retention syndrome (blood urea nitrogen (BUN) and creatinine measurements) is severe, and constantly present. This is associated with metabolic acidosis, nephritic changes in the urinary sediment (albuminuria, hematuria), hydroelectrolytic disparity typical for anaemic persons (hypo/hypernatremia, hyperkalemia, hypocalcaemia accompanied by hyperphosphatemia).

Bone marrow aspirate shows erythroid hyperplasia and increased megakaryocytes.

The stool typically indicates the presence of *E coli* or other bacteria.

Verotoxin can be detected in patient's stool by PCR test.

Definitive diagnosis

The diagnosis is confirmed by the presence of microangiopathic haemolytic anemia, thrombocytopenia and acute renal failure, usually in children younger than 5 years of age, with recent history of diarrhoea or respiratory episode, and typical laboratory changes.

Differential diagnosis

There are diseases that due to similar symptoms (acute renal failure and microangiopathic haemolytic anemia), may be taken for HUS: systemic lupus erythematosus, malignant hypertension (in older children).

HUS may be difficult to differentiate from bilateral renal thrombosis; both diseases are preceded by an episode of acute gastroenteritis and both have similar clinical representations (dehydration, pallor, microangiopathic haemolytic anemia, thrombocytopenia, and acute renal failure). In order to establish the diagnosis, a renal Doppler ultrasound and/or an angiography should be performed.

Other entities include sepsis, purpura fulminans, chronic haemolytic anemia, G6PD deficiency, thrombotic thrombocytopenic *purpura (Moscowitz*), *disseminated intravascular coagulation, and* antiphospholipid syndrome.

Complications

Possible complications of HUS include: severe anemia, metabolic acidosis, heart failure, hypertension, and uraemia.

Extra renal complications associated with HUS may involve the central nervous system (irritability, seizures, thrombosis, altered mental status), the gastrointestinal system (colitis, gastrointestinal bleeding, perforation), retinal haemorrhages, and rhabdomyolysis. These complications appear to be the result of intravascular thrombosis.

Treatment

The HUS therapy is mainly supportive and it *varies with the severity of the disease.* Patients with HUS may require multidisciplinary collaboration in an intensive care unit: infectious diseases specialist, haematologist, pediatric nephrologist, and even a kidney transplant team (in extreme cases).

The aim of the treatment is to monitor and support the functions of the affected organs and systems: acute renal failure, hematologic and neurologic disorders.

1. Monitoring acute renal failure in patients with oligo-/anuria:
   - Close monitoring of fluid intake and diuresis
   - Documentation of body weight each 12-24 hr
   - Measuring plasma concentrations of Na, K,

Cl, HCO3, pH and pCO2 every 4-8 hr
- Determination of plasma concentrations of urea nitrogen, creatinine, proteins, calcium every 8-12 hr
- Daily urinalysis (albumin, glucose, sediment, NA, K, Cl)

2. Monitoring of haematologic abnormalities:
   - Complete blood count every 12-24 hr; examination of erythrocyte morphology on peripheral blood smear
   - Coagulation tests to exclude *disseminated intravascular coagulation*
   - Exclusion of other causes of haemolytic anaemia (Coombs test, G6PD deficiency)
3. The monitoring of nervous central system (CNS) disorders has two goals: to establish if the brain's functions are preserved, and to assess the impairment of CNS.
   - The conscious state of the patient (Glasgow coma scale)
   - *Pupil dimensions and reactivity*
   - Type and frequency of convulsions
   - Eye examination, EEG, head CT or MRI

The restriction of the parenteral fluids intake should be strictly adapted according to diuresis, thereby controlling hypertension and cerebral oedema.

Also, metabolic acidosis and electrolytic abnormalities should be corrected by administrating 84% natrium bicarbonate and molar solutions of 74% KCl, 58,5% NaCl, 10% calcium gluconate.

The administration of fresh frozen plasma is useful and it is performed daily, until remission (85% of the children with haemolytic-uremic syndrome recover after supportive therapy alone).

When needed, blood transfusions prevent hypoxemia, cardiac impairment and severe anaemia.

Patients with *pneumococc*al associated *HUS* risk a worsening of the disease with *blood* product *transfusions (*this is secondary to the infusion of antibodies).

The plasmapheresis is not completely evaluated in HUS, but has successfully been used in treating thrombotic thrombocytopenic purpura in adults and it may be indicated in children with recurrence of HUS.

The recommendation is to avoid the unnecessary use of antibiotics (except in cases of sepsis) or anti-motility agents, since the gut will be exposed to the toxins for a longer period of time.

In children with persistent oligoanuria, severe fluid-electrolyte and acid basic imbalance and high nitrogen retention, haemodialysis is urgently required. In severe cases, it is indicated to consider consulting the renal transplant service.

Refractory cases have been treated with vincristine or cyclosporine; corticosteroids and antiplatelet agents such as aspirin and dipyridamole may also have some therapeutic benefits.

Fibrinolytic therapy is not only ineffective, but it may also increase the risk of bleeding.

Recent studies have been performed to evaluate new potentially useful alternatives in the treatment of HUS, such as drugs that block the action of verotoxin in the gastrointestinal tract (Chromosorb) or neutralise it (Starfish).

Prognostic

After recovery, patients with HUS should be monitored for a long period of time in order to control hypertension caused by the renal disease and chronic renal insufficiency.

Approximately 90% of the patients with acute renal insufficiency are cured, and their renal functions are fully restored after treatment

The mortality rate of HUS is 12% (it may increase to 40% without appropriate treatment).

In patients with severe forms of the disease, long-term consequences such as proteinuria, hypertension and progressive renal insufficiency are present.

Recurrence of HUS with severe prognosis of the renal function is possible.

As physicians treating infectious diseases, we have diagnosed HUS associated with acute diarrhoea. It was not the diagnosis that was difficult, but the choice of therapy, in a clinic with an intensive care unit and the possibility of renal dialysis at any time.

We will now shortly present a case of HUS associated with diarrhoea with *E coli* enteropathogen. Since the patient had to be urgently transferred, the required tests could not be performed.

Case Report

A 3-year old girl was admitted at The National Institute of Infectious Diseases "Prof. Dr. Matei Balş" with intense abdominal pain, nausea, loss of appetite, and frequent bloody watery diarrhoea.

The patient's medical history did not reveal anything significant, except for a twin brother with diarrhoea.

The past medical history was non-contributory:

preterm delivery, 7 months twin pregnancy, natural birth. She was breastfed for one month. The immunization schedule appeared to be normal. The neuropsychic development was normal.

Twenty-four hours prior to admission, the patient developed progressive lower abdominal pain, loss of appetite, and severe watery diarrhoea. Symptomatic medical therapy was prescribed, but it was ineffective and the symptoms worsened during the next 12 hours, when the patient developed bloody diarrhoea.

Physical examination on arrival: temperature 36.9°C, pulse 92 bpm, slightly altered clinical state, pale face, no skin eruption, slightly reduced skin turgor, slightly sunken eyes, submandibular adenopathy, mild nasal obstruction, unaltered pulmonary sonority, dry tongue, loose abdomen, marked diffuse abdominal tenderness, watery bloody stools, untouchable liver and spleen, and no meningitis syndrome.

Laboratory findings include:

- Erythrocyte sedimentation rate 20mm/h, fibrinogen 331mg/dl; serum concentrations of urea, creatinine, sodium, potassium, glucose, ALT, and AST were normal.
- No bacteria from nose and throat swabs were isolated in culture. The enteropathogen *E coli* was identified in the stool culture. Shigella and Salmonella were not identified. No viruses were seen in stools.

Hemogram:

- April 13th 2009 – leukocytosis (14.000/cmm) with neutrophilia (75.9%), low lymphocytes (13.2%), hypochrome anemia (red blood cells 4.290.000/cmm, haemoglobin 11.4g/dl, hematocrit 33.8%, MCV 78.7 fl, MCH 26.7 pg), thrombocytopenia (152.000/cmm);
- April 15th 2009 – red blood cells 2.850.000/cmm, haemoglobin 7.1g/dl, hematocrit 21.4%, platelet count 27.000/cmm.

The peripheral blood smear revealed thrombocytopenia.

Treatment consisted of management of dehydration (i.v. infusion), antibiotic therapy (Cefuroxime 375mg/8h, i.v.), and symptomatic therapy.

Over the next 2 days the patient's condition deteriorated. The abdominal pain gradually lessened, but the clinical status worsened, and the patient developed altered mental status, started vomiting, and the frequency of bloody watery stools increased.

The physical examination performed on the third day showed deeply sunken eyes, dry lips, parched mouth and tongue, and decreased skin turgor.

Patient's haemoglobin levels fell to 7.4 – 7.1g/dl, the platelet count to 36.000 – 27.000/cmm. Serum urea concentration increased to 126 – 130mg/dl (normal value 10.8 - 36mg/dl), plasma creatinine increased to 1.7mg/dl (normal value 0.5 – 1.4mg/dl), and the CBC showed haemolytic anemia.

Despite adequate hydration, the patient's urea and creatinine values remained elevated. The patient was diagnosed with HUS based on haemolytic anemia, thrombocytopenia, and acute oliguric renal failure. The patient was transferred to the Intensive Care Unit at the "Fundeni" Hospital in order to receive emergency medical treatment (haemodialysis).

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