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Review Article

Haemolytic Uraemic Syndrome (HUS): Clinical Medicine Versus Clinical Anatomy

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Abstract

Haemolytic Uraemic Syndrome (HUS) is an acquired disorder affecting mainly infants and children. The triad of this clinical syndrome is defined by: 1) Thrombotic or Microangiopathic Haemolytic Anaemia with schistocytes 2) Thrombocytopenia and 3) Acute Renal Failure (ARF) which can develop into Chronic Kidney Disease (CKD). The aim of this article is to provide an editorial/commentary on the Clinical Medicine versus Clinical Anatomy of HUS.

HUS is the most common cause of Acute Renal Failure (ARF) in children with an equal sex incidence [1]. The annual incidence of VTEC infection varies geographically; it can range from 1 to 30 cases per 100,000 in industrialized countries. It is a rare syndrome post-puberty but it is also closely related to Thrombotic Thrombocytopenia (TTP) which is common in adults. The annual incidence of the Verocytotoxin-producing *Escherichia Coli* (VTEC) infection varies geographically from year to year, ranging from 1-30 cases per 100,000 in industrialized countries and is associated with HUS. HUS occurs in sporadic cases epidemics; between 1st January [2] and 31st December [2] in England, a total of 3717 cases were reported with evidence of Shiga Toxin-Producing *E. Coli* (STEC) infection; sometimes following outbreaks. In Hamburg [3], there was an outbreak with more than 900 cases. The disease has seasonal variation, being more common in the warmer months in children.

Renal histopathology is characterized by abnormal morphology applicable to afferent arterioles and glomeruli. The glomeruli show evidence of global sclerosis and glomerular thrombotic microangiopathy endothelial cell swelling; capillary wall thickening and glomerular basement membranes also evident. Interstitial fibro edematous change and tubular atrophy are marked. Arterial, arteriolar and capillary lumina are narrow with obstruction and intimal thickening. The nature of vascular involvement in the kidneys supports the hypothesis that HUS is mediated by systemic toxemia and endothelial cells are the primary target cells owing to action of Verocytotoxin. Histopathological findings provide clues not only to the diagnosis but also in the support of prognosis. Diffuse tubular interstitial change and global sclerosis indicate the degree of blood flow obstruction and prognosis. Renal blood flow obstruction caused by diffused arterial and arteriolar luminal stenosis may lead to irreversible changes in renal pathology

Keywords: Haemolytic Uraemic Syndrome (HUS); Clinical medicine; Clinical anatomy; Chronic kidney disease; Acute renal failure; Haematology

Introduction

Haemolytic Uraemic Syndrome (HUS) occurs due to Shiga-like toxin activity *via* aberrant complement activation. HUS is typically classified into two primary types: 1) HUS due to infections, often associated with diarrhoea (D+HUS, Shiga toxin-producing *Escherichia Coli*-HUS), with the rare exception of HUS due to a severe disseminated infection caused by *Streptococcus*; 2) HUS related to complement, such HUS is also known as "atypical HUS" and is not diarrhoea associated (D-HUS, aHUS) [4]. Clinical features include proteinuria, renal impairment and history of *E. coli* diarrhoea (hallmark of typical HUS). Encephalopathy is rare but can cause death. HUS is seen increasingly following outbreaks of infection with Verotoxin (VT)-producing organisms. It represents a growing public health problem and data suggest that more awareness of specific

micro-organisms causing diarrhoea, (and those thus leading to HUS and/ or HUS related symptoms) may become more important in future health consultations [3].

E. coli 0157:H7 is the most commonly notified VT-producing organism in the UK and France. Clinical manifestations may vary from an asymptomatic infection to bloody diarrhoea, haemorrhagic colitis and HUS. Verotoxin Enterococcal (VTEC)-associated HUS was seen in up to 20% of patients in recent outbreaks, mainly affecting children [5]. Table 1 summarizes the defining classification of HUS and (Table 2) summarizes features of HUS, respectively.

HUS epidemiology

HUS is the most common cause of Acute Renal Failure (ARF) in children with an equal sex incidence [1]. The annual incidence of

Table 1: Classification of HUS.

HUS - Classifications
Typical
Infection related
Shiga toxin producing <i>E. coli</i> / <i>Shigella</i>
Pneumococcal infection
HIV
Other viral or bacterial infections
Atypical
Complement factor abnormality
Factor H deficiency and Factor I deficiency
Miscellaneous
Cumulative Trauma Disorder (CTD), drugs, malignancy

Table 2: Defining features of HUS.

HUS - Defining Features
<ul style="list-style-type: none"> Renal involvement Evidence of coagulopathy –intravascular coagulation in the kidney Antipathy - marked fragmentation of red cells The disorder is associated with activation of neutrophils Typical HUS is secondary to GI infection with Verocytotoxin-producing <i>E-coli 0157:H7 (VTEC)</i>, less often <i>Shigella</i> Complement activation used to attack foreign bodies Complement system highly regulated to prevent it from damaging healthy tissues/ organs Platelet activation, damage to endothelial cells (cells that line the blood vessels), white blood cell activation causing haemolysis Thrombotic Microangiopathy (TMA) – formation of blood clots in small vessels throughout the body and over time, causing multiple organ damage
Table adopted from (Blaser 2004; Licht et al. 2009)

Table 3: HUS signs.

HUS - Signs
<ul style="list-style-type: none"> Patients present with anaemia Petechiae, purpura, and fever are common GI bleeding is often found and a bloody diarrhoea GI disease may be severe with haemorrhagic colitis, toxic megacolon, rectal prolapse, and bowel necrosis Neurological symptoms Cardiac involvement may lead to Congestive Heart Failure (CHF) and arrhythmias Microinfarcts in the pancreas (pancreatitis) or, rarely, Insulin Dependent Diabetes Mellitus (IDDM)
Table adopted from (Licht et al., 2009)

VTEC infection varies geographically; it can range from 1 to 30 cases per 100,000 in industrialized countries. There is seasonal variation, thus being more common in warmer months. It is more common in those under 5-years.

Between 1st January [6] and 31st December [6] in England, a total of 3717 cases were reported with evidence of Shiga Toxin-producing *E. Coli* (STEC) infection, and the crude incidence of STEC infection was 1•80/100 000 person-years. Incidence was highest in children aged 1-4 years (7•63/100 000 person-years) [2].

HUS diarrhoea association

Most common cause of HUS and intrinsic ARF in paediatrics in the UK, France and USA industrialized countries is diarrhoea. There are no specific therapies to treat the diarrhoea. Mortality is as high as 8.5 % and up to 30 % of survivors may develop further Glomerular Filtration Rate (GFR) impairment or albuminuria [6].

Use of anti-motility drugs may increase the risk of developing

Table 4: HUS symptoms.

HUS - Symptoms
<ul style="list-style-type: none"> The kidneys are swollen and pale Many flea-bite hemorrhages are on the surface GI involvement may lead to symptoms of an acute abdomen, with occasional perforation Hypertension Anuria – Oliguria, depending on overall GFR/ renal function
Table adopted from (Licht et al., 2009)

Table 5: HUS – Haematology.

HUS - Haematology
Full Blood Count (FBC) highlights an anaemic picture on presentation
Coagulation highlights APTT and PT are both normal - suggests sepsis rather than HUS/TTP
Platelet and fibrin micro-thrombi is evident within the renal microvasculature
Thrombocytopenia is universal at some point in the illness
Haematinics highlight there is variability in Iron titres
Direct Coombs Test is Negative
Plasma Haptoglobin levels is decreased owing to Red Blood Cell (RBC) breakdown/ degradation
Raised Fraction Degradation Products (FDPs)
There is a slightly elevated D-Dimer
There may be microcytosis
Red cell enzymes and osmotic fragility are normal
Reticulocyte count is elevated
Table adapted from (Taylor et al., 1999; Taylor 2001a; Taylor 2001b; Taylor et al., 2004)

HUS and it is a rare syndrome post-puberty [1]. Atypical HUS (aHUS) can be inherited or acquired and does not appear to vary by race, gender or geographic area. Data on the prevalence of aHUS is limited [7,8] (Table 3).

HUS and laboratory tests/ investigations

Haemolysis and red cell fragmentation are usually evident at presentation, although this rarely develops later in the disease even after platelet count improvement (Table 4). Coagulation studies are usually normal with mildly raised D-dimer titres in contrast to Disseminated Intravascular Coagulation (DIC) [9]. The Von-Willebrand Factor (VWF) levels are usually markedly raised during acute illness while analysis may/ may not show ultra-large multimers [10]. Poor prognostic features at presentation include a high neutrophil count [11]. Severe thrombocytopenia is uncommon but prolonged thrombocytopenia for more than 10 days is associated with long-term renal picture. Factor VIII levels do not correlate with clinical outcome [12]. Table 5 summarizes laboratory tests/ investigations according to Haematology specialty. Figure 1 depicts HUS red cell morphology under microscopy.

Prognosis and treatment

Treatment is by supportive measure, and the main treatments are either Haemodialysis (HD) or Peritoneal Dialysis (PD) because of the ARF. The prognosis is dependent upon the aetiology and renal function; there is a poor prognosis if patient requires HD or PD more than 7 days, but good prognosis is conceivable with total recovery of renal function with no arterial hypertension, and no proteinuria. Children with intra-cerebral involvement may be treated with plasma

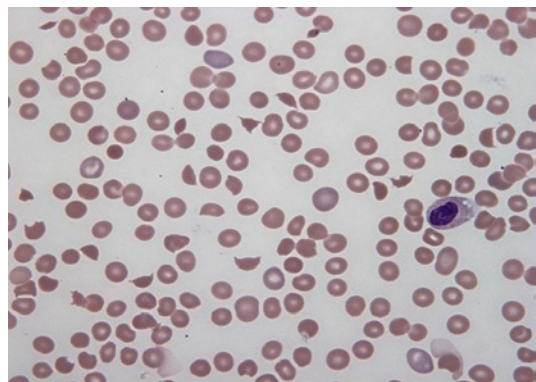


Figure 1: HUS red cell morphology under microscopy. RBC fragmentation with obvious schistocytes/ helmet cells. Note decrease in platelets which is a typical picture in HUS patients. Schistocytes are irregularly shaped fragments with two pointed ends without central pallor (Barcellini & Fattizzo 2015). Slide taken from (<http://medicine.medscape.com/article/779218-workup>) (accessed December 2016).

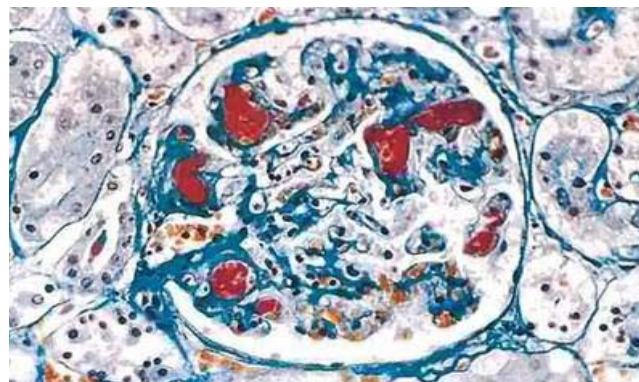


Figure 3: HUS - fibrin histological stain. Fibrin histological stain highlighting platelet-fibrin thrombi (red) in the glomerular capillaries, characteristic of HUS/microangiopathic disorder, (taken from <http://slideplayer.com/slide/11018533/>) (accessed December 2016).

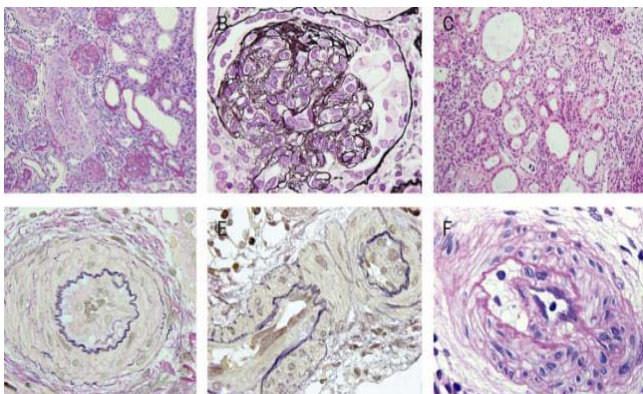


Figure 2: Histological Stains of a Kidney Biopsy Specimen – Day 37 following Eculizumab Treatment characteristic of a HUS. **(A)** Almost all glomeruli give evidence of global sclerosis or collapse (Periodic Acid Schiff stain [PAS]; $\times 100$). **(B)** Endothelial swelling is conspicuous and glomerular basement membranes are focally duplicated (Periodic Acid Methenamine silver stain [PAM]; $\times 1000$). **(C)** Interstitial fibroedematous change and tubular atrophy are marked (Haematoxylin and Eosin stain [H&E]; $\times 200$). **(D, E)** Arterial and arteriolar lumina stenosed or obstructed with intimal thickening (Elastic van Gieson stain [EVG]; $\times 1000$). **(F)** Mononuclear cells infiltrated into intima of arteries (PAS $\times 1000$). These findings are helpful demonstrating the diagnosis of TMA diagnosis (Slide stain taken from Okuda et al. 2015).

Table 6: HUS key haematology morphological features.

HUS – Key Morphological Features
Peripheral blood smear depicts striking red cell fragmentation
Findings of microangiopathic haemolytic anaemia
Deformed, irregular or helmet-shaped RBCs – schistocytes
Thrombocytopenia (counts of $50 \times 10^9/l$) or less
Neutrophil may be quite marked – it is a marker of adverse prognosis
Polychromasia (greyish tinge) may be marked
Bone Marrow is cellular – response to haemolysis/ red cell breakdown
Table adapted from (Taylor et al., 1999; Taylor 2001a; Taylor 2001b; Taylor et al., 2004)

Table 7: HUS– chemistry/ microbiology.

HUS - Chemistry
Urea, Creatinine and Electrolytes demonstrate abnormally high results
Urine, if present, may contain protein and RBCs
Liver Function Test (LFTS) can be normal
Urine dipstick can show some protein leaking (24hr urine collection needed to quantify)
Electrophoresis can be helpful and important to establish extent of protein leaking
Blood Urea Nitrogen (BUN) is markedly elevated
HUS - Microbiology
Cultured species of E-coli is performed
Mainly looking for group Enterohaemorrhagic E-Coli (EHEC)
(Table adapted from Taylor et al., 1999; Taylor 2001a; Taylor 2001b; Taylor et al., 2004)

exchange, but efficacy and long-term use is not advisable [13-15].

Major neurological dysfunction occurs in a third of patients in atypical HUS and less than 10% in typical HUS; is associated with a poor prognosis [7]. There should be supportive information made available for the patient and parent or career/guardian. Eculizumab is a monoclonal antibody that binds to C5 to prevent the formation of C5a and the membrane attack complex [7,8]. This treatment has become popular and can be helpful for patients who may have extra renal involvement such as that seen in typical HUS. Its efficacy and safety in the treatment of aHUS has been highlighted recently [7,8].

Management

Either HD or PD treatments is essential when renal function is altered. It is crucial to control hypertension, thus preventing

any longer term complications (Figures 2 and 3). RBC transfusion in children is common owing to anaemia [13-15]. Fraction Frozen Plasma (FFP) has been administered in adults [8].

Research perspectives

Haemoglobin (Hb) is the most direct indicator of clinical severity in haemolytic diseases. Its level may be close to normal values in mild forms (Hb >10 g/dL) or reduced in moderate (Hb 8–10 g/dL), severe (Hb 6–8 g/dL), and very severe (Hb 6 g/dL) forms (WHO 1989). In a differential diagnosis, an acute onset is more frequently observed in RBC enzymopathies involving the Pentose Phosphate (PP) shunt

Table 8: HUS key anatomical/histopathological features.

HUS – Key Histopathological Features
Afferent arterioles and glomeruli inflammation
Ischaemic necrosis in renal cortex may occur from intravascular coagulation
Glomerular thrombosis and sclerosis
Hypercellularity
Sclerotic tuft
Fibrinous necrosis in places and some tubule-interstitial compartments show atrophic changes with infiltration of the inflammatory cells
Endocapillary swelling with diffuse arteriolar and arterial luminal stenosis due to the thickness and sclerotic changes of the media and intima
Renal Scarring
Table adapted from (Taylor et al., 1999; Taylor 2001a; Taylor 2001b; Taylor et al., 2004; Okuda et al., 2016)

(e.g. glucose-6-phosphate-dehydrogenase, G6PD deficit) and in autoimmune haemolytic forms involving complement activation Autoimmune Haemolytic Anaemia (AIHA) caused by warm IgM, warm IgG + C, mixed, and Cold Agglutinin Disease (CAD) (with thermal range close to physiological temperatures) and in Paroxysmal Nocturnal Haemoglobinuria (PNH) (Tables 6,7 and 8).

Summary

Clinical medicine

- Bloody diarrhoea still most crucial element to be aware of in young patients
- Renal Function over time must be monitored
- Haemolytic parameters may be differently altered in the various conditions thus helping the differential diagnosis and coagulation must be monitored
- LDH is useful in evaluating response to treatment, as its level decreases along with the reduction of the haemolytic rate
- Polynucleosis is a factor of poor prognosis

Clinical anatomy/histopathology

- Glomerulus: hyalinized, thickened and sometimes split capillary walls due to endothelial swelling
- Tubules: atrophied and contains hyalinised casts
- Interstitium: fibrosed with lymphocytic infiltration
- Vessels: arterial and arteriolar sclerosis, intimal hyperplasia and fibrinoid necrosis with large deposits of fibrin-related materials in the capillary lumen. They are often occluded by thrombi.

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This article is dedicated in loving memory to a dear friend Emma Marquik (1975 to 2003) who went through the whole HUS triad – Fourteen years on a Haemodialysis protocol and three transplants is what took her life.

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