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Editorial Review

The Hemolytic Uremic Syndrome

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The triad of thrombocytopenia, microangiopathic hemolytic anemia and acute nephropathy characterises the hemolytic uremic syndrome (HUS) The name was given by Gasser and coworkers in 1955. with the belief that future studies would reveal a variety of causes, pathogenic mechanisms and subsets of this syndrome[1]. HUS has been reported from many parts of the world, mainly USA, Britain, France, Argentina, Netherlands and South Africa[2-6]. Cases have also been reported from Bangladesh, India[7] and more recently Pakistan[8]. Affecting mainly infants and children under 2 years of age, the disease has become one of the most important causes of acute renal failure in children, and generally follows an episode of bloody diarrhea[9-11]. Although many bacteria, viruses, some cytotoxic drugs have been implicated, etiology and predisposing factors remain unclear.

The following subgroups of HUS are seen in children.

A) Typical

By far the commonest group, it is usually associated with diarrhea, and affects infants and young children[12-14]. It often occurs in epidemics, in the summer[14,15]. When it follows shigella dysenteriae infection, it is seen in developing countries, and carries a worse prognosis[16].

B) Atypical

Also referred to as sporadic HUS or non-diarrhea associated HUS, it affects children of all ages and may follow a relapsing or progressive course[18-19].

Etiology

The clinical and epidemiologic features of typical childhood HUS suggest an infectious cause and a wide variety of pathogens, bacteria as well as viruses have been implicated. The viruses included in the list are coxsackie A4, B2, or B1, Echo, influenza and EBV[20-22]. The proof that viruses are in fact involved in the pathogenesis of HUS is at times anecdotal and generally not reproducible. Individual cases or small outbreaks of HUS have reportedly been associated with Salmonella[23], Campylobacter[24] Yersinia[25] and the pneumococcus[26] Karmali in 1983 reported that eight of 15 patients with HUS had the presence of infection with *E. coli* strain 0157:H7, which produced a cytotoxin toxic to Vero Cells[27] The association of verotoxin-producing organisms and HUS was subsequently confirmed from Canada[28] USA[29,30] and UK[15] It was found that infection with this organism frequently preceded HUS and that the organism produced massive amounts of toxin closely related to shigatoxin[31]. Even prior to the association of verotoxin producing *E. coli* with HUS, the *E. coli* producing this toxin had been implicated in the pathogenesis of hemorrhagic colitis. The commonest organism identified in hemorrhagic colitis was also *E. coli* 0157:H7[32,33]. In most of the reported outbreaks of hemorrhagic colitis a small proportion of affected persons developed HUS.

Over the last few years, there has evolved a knowledge of the biology of verotoxin producing organisms and their role in HUS[34]. Initially it was considered that there was a single cytotoxin closely related to shigatoxin, that was produced by all cytotoxin producing *E. coli*. These toxins which can be neutralized by antibody to shigatoxin are called shigalike toxin (SLT-I) or verotoxin I. SLT I is identical to toxin produced by Shigella dysenteriae I[35,36]. Further, the demonstration that the same toxin could also be produced by other enteric pathogens suggests that verotoxin or related toxins are responsible for HUS seen in association with several different organisms[34,37].

Because of the association of HUS with bloody diarrhea, attention has also focussed on shigella dysenteriae I. This pathogen was reported first from Central America[38]. Subsequent reports have appeared from Bangladesh and India[39,10]. These children tend to be sicker and carry a high mortality[16]. Shigella dysenteriae I produces Shigatoxin, a cytotoxin shown to cause fluid accumulation (often hemorrhagic) in the tied off segments of rabbit ileum, kills mice when inoculated intraperitoneally and kills certain mammalian cells in tissue culture[41,42]. Although other serotypes produce toxin, the concentration of Shigatoxin is

higher with shigella dysenteriae type I which is also the commonest cause of dysentery[13].

Pathogenesis

Due probably to the heterogeneity of the disorder, many different theories have been proposed to explain the pathogenesis in HUS. The first to receive attention was the activation of the coagulation pathway as a primary event[14-16]. In general, factor V and VIII levels are either normal or slightly elevated, Prothrombin time normal and partial thromboplastin time normal or slightly prolonged. Fibrin degradation products are raised and antithrombin III levels may be reduced. Consumption of factor VIII has been seen[17-50] Disseminated intravascular coagulation was postulated as an important event specially in most cases of shigella-associated HUS[16]. Subsequent studies failed to confirm the importance of activation of coagulation in typical HUS[51,52].

Intravascular platelet activation and increased platelet destruction occurs in all types of HUS, as documented by shortened platelet survival and platelet degranulation[53-55]. Plasma levels of platelet derived factors such as serotonin, platelet derived growth factor and thromboglobulin are increased and their intraplatelet concentrations diminished[53]. Intravascular platelet activation continues for several weeks after the platelet count has returned to normal in both typical and atypical subgroups of HUS. Most attempts to explain the platelet activation have either suggested abnormalities of the integration between platelets and the vascular endothelium or the presence of circulating platelet-aggregating factors[56].

Remuzzi in 1978 implicated abnormal endothelial production of prostacyclin in the pathogenesis of HUS[57] Prostacyclin is an endogenous prostaglandin with an inhibitory effect on platelet aggregation[58] Decreased production of prostacylin (as with endothelial injury) can cause platelet aggregation and microthrombi formation. Although other studies have confirmed reduction in prostacyclin production after incubation of endothelial cells with HUS plasma, children with typical diarrhea associated HUS may have normal prostacyclin production[53,56,59]. Of therapeutic significance is the response of HUS patients to fresh plasma infusions or plasmapharesis[60]. However, in a recent multicentre trial, evaluating the role of plasma infusion in children with HUS, no difference was found between the group receiving plasma infusion and the group on symptomatic therapy[61].

Although neither platelet activating factors nor prostacyclin deficiency adequately explain the platelet activation in typical HUS, there is growing evidence that the platelet or the red blood cell destruction is related to contact with damaged endothelium and that the primary insult is to the endothelial cell. Endothelial cell swelling and separation of endothelial cells from the basement membrane, with reduction of the capillary lumen has been shown, following intravenous injections of verotoxin to rabbits[62]. Endothelial cells express Gb3, the receptor for verotoxin and it has been demonstrated that the toxin has a dose-dependent cytotoxic effect on cultured endothelial cells[63]. It has been proposed that the toxin may bind to receptors on the endothelial cells in the gastrointestinal tract, kidney and brain and damage or destroy cells. Platelets and red blood cells are then disrupted secondarily by mechanical forces during passage through the damaged capillary endothelium[64].

Besides direct toxin-mediated insult, factors such as direct red blood cell membrane damage[65] and white cell mediated toxicity[66] may be important, specially in view of the leukocytosis and leukemoid reactions observed in shigella-associated HUS[16] Although leukocytosis may indicate greater severity of inflammation, leukocytes may release oxygen free radicals and proteolytic enzymes on activation, causing damage to the endothelial cells[67,68].

Clinical Picture

HUS occurs primarily in infants and young children, generally under 3 years of age[69]. Neonatal cases are rare and in adults, cases are reported secondary to the use of oral contraceptives or with hypertension. White children are affected more often than blacks[70]. Although genetic factors have been implicated, no common genetic marker is documented[10].

Affected children are usually healthy before the onset of HUS when they develop gastrointestinal symptoms (non-specific with vague abdominal pain, diarrhea-often bloody) or acute respiratory infection[12]. Children may present with acute abdomen, simulating acute appendicitis, or intussusception[71,72]. The mild prodrome is followed in 7-10 days by onset of pallor, purpura, acute diarrhea (often bloody) oliguria and hematemesis. In severe forms, hypertension and seizures often

complicate the picture and anuria lasting days to weeks is the rule.

Besides seizures, serious complications such as hemiparesis, decerebrate posturing and coma may be seen. These CNS manifestations generally imply a poor prognosis and a high mortality[73]. Similarly jaundice may be seen in 15-30% children, reflecting hepatic involvement[71]. Pericardial, myocardial and pulmonary involvement has been observed and congestive cardiac failure due to volume overload and hypertension are serious cardiovascular consequences.

There is good correlation between the severity of the renal involvement and the ultimate outcome-prolonged anuria or oliguria and persistence of hypertension usually imply a poor prognosis. Recovery of renal function may take 2-3 weeks, although 12-18 months may elapse before complete renal recovery.

Investigations

The important investigations are as follows:-

1. *Hematologic studies*[75]

The hemoglobin level is decreased, suggestive of the underlying hemolysis. The peripheral smear reveals fragmented RBC's, burr cells, helmet cells, teardrop cells and microspherocytes. RBC survival time is shortened with a high reticulocyte count, low or absent plasma haptoglobulin, high bilirubin and occasional hemoglobinuria.

The leucocyte count is elevated as a rule with predominant polymorphonuclear cells, although leucopenia is seen occasionally[12]. Thrombocytopenia is the hall-mark of HUS and may persist for 2 weeks[31]. There is increased platelet destruction, with increase in plasma PL factor 4, platelet activating factor, platelet aggregation and thromboxane. Prostacyclin levels and platelet Beta Thromboglobulin are decreased[12]. Prothrombin time, fibrinogen and FDP are usually increased[75].

2. *Electrolyte and Metabolic Abnormalities*

There is usually evidence of hyperkalemia, alongwith increased BUN and serum creatinine. The calcium level may be low or is raised occasionally. Hyperlipidemia and hyporoteinemia are also seen.

3. *Renal Abnormalities*

Urinalysis reveals proteinuria, hematuria and occasionally hemoglobinuria.

4. *Immunological Profile*

The complement levels (C1q, C3, C4, CH50, Factor B, Factor D) may be decreased, although C5 level is normal.

Management

There is no universal agreement on the treatment modalities of HUS, but early recognition, with awareness of potential complications is helpful in bringing the mortality down to <10% in developed countries.

Supportive therapy includes management of fluid and electrolyte balance, packed cell transfusion as needed, nutritional support and control of complications (seizures, hypertension). Special emphasis needs to be placed on correction of hyponatremia and hyperkaemia and of hypocalcemia and hyperphosphatemia[76]. Hypertension is best managed by the use of Hydrallazine and Nifedipine. Seizures may require the use of Diazepam intravenously and Phenytoin.

The control of azotemia, however, is most critical. As a consequence of renal insufficiency, catabolism and reabsorption of blood from the gastrointestinal tract the BUN may begin to rise at a rate more than 50 mg/dL/day. Early dialysis has been advocated to limit azotemia and generally agreed indications are:

1. BUN > 100 mg/dL.
2. Anuria > 24 hours.
3. Serum Potassium > 7mEq/dL on two occasions within 24 hours.
4. Serum Bicarbonate < 12 meq/dL.
5. Hypernatremia (serum Sodium > 150 mEq/dL).
6. Hypocalcemia (serum calcium < 7 mg/dL)
7. Hyperphosphatemia (serum phosphorous > 15 mg/dL).
8. Pulmonary edema.
9. CNS involvement (seizures, stupor, coma)

However, prophylactic dialysis has been advocated by some authors and may be started as soon as diagnosis is established[12]. Where there is documented evidence of infection with Shigella, antibiotics may be given, keeping in mind the

sensitivity pattern. It may be pointed out that there are reports of an association between antibiotic administration and the development of HUS in Shigella infection[77] and in verotoxin-associated HUS[30].

Specific Treatment

Keeping in mind the various factors implicated in the pathogenesis of HUS, many attempts have been made to reverse the microangiopathic process by specific treatments such as:-

1. Anticoagulation therapy[78]
2. Fibrinolytic agents[79]
3. Antiplatelet drugs[80]
4. Prostacyclin[81]
5. Vitamin E[82]
6. Plasmapheresis[83,84]
7. Fresh plasma infusions[85]
8. Intravenous immunoglobulins (IgG)[86].

However, controlled trials using the above modalities of treatment has not shown any significant improvement[61].

Prognosis

The current mortality has been reduced to under 10% mainly with early dialysis[2]. Bed prognostic factors include[87].

1. Age over 24 months.
2. Non-diarrheal prodrome.
3. Familial involvement with evidence suggestive of recessive or dominant inheritance.
4. Being an adult.
5. Progressive reduction in renal function or renal failure greater then 2-3 weeks duration.
6. Reappearance of hemorrhagic phenomenon after 10 days of illness.
7. Persistent leucocytosis.
8. Persistent or recurrent thrombocytopenia.
9. Severe CNS involvement.
10. Persistently low serum compliment levels.

Generally of those with typical HUS, most (18%) recover completely but only 22% of the children with atypical HUS recover[88]. The prognosis in Shgella-associated HUS has usually been worse[77] although it may have to do with the fact that this form occurs more in under-developed countries often in malnourished children, with fewer facilities.

Risk Factors

Risk factors for progression of an episode of diarrhea to HUS have not been clearly elucidated. In a retrospective case-control study of 30 children with shigella dysenteriae I infections, Butler showed that previous treatment with antibiotics (Ampicillin TMP-SMZ) and elevated leukocyte count were factors associated with the development of HUS[77] Cimolai identified, again in a retrospective analysis, an association between young age and prolonged antimotility agent use with progression of *E. coli* 0157:H7 enteritis to HUS[89,90].

In a study of prognostic factors, young age, preceding diarrheal episode, presentation during summer, a short prodromal illness and early dialysis were considered to carry a better outcome[2] whereas Lane in 1988, reported a poor prognosis with an elevated white blood count, prolonged period of thrombocytopenia and anuria[91]. In this report, young age was associated with poor prognosis.

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