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Occasional survey

Extrarenal involvement in diarrhoea-associated haemolytic-uraemic syndrome

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Abstract. A review of extrarenal involvement in diarrhoea-associated haemolytic-uraemic syndrome (HUS) is based on 64 of our autopsied patients and an update of the literature.

Large bowel pathology was the commonest (29 cases), followed by the central nervous system (21 cases), the heart (19 cases) and the pancreas (19 cases). The severity of systemic involvement was associated with the magnitude of renal compromise and the prognosis of the acute phase. Diarrhoea-associated HUS is described as a multiorgan entity, due to extensive microvascular damage and thrombosis. At present mortality during the acute phase is not confined to renal failure; systemic involvement can also lead to death.

Key words: Haemolytic-uraemic syndrome – Thrombotic microangiopathy – Extrarenal involvement

Introduction

In early reports descriptions of the classic haemolytic-uraemic syndrome (HUS) were limited to the association of haemolytic anaemia, thrombocytopenia and acute renal dysfunction [1, 2]. Study of a larger number of cases allowed the importance of non-renal involvement to be defined [3]; this is now considered to comprise a systemic thrombotic microangiopathy (TMA) related to a specific gastrointestinal infection [4]. The great advances in the treatment of acute renal failure (early dialysis and eventual transplantation) have resulted in a marked reduction in mortality due to renal failure during the acute phase of HUS and have led to increasing interest in the clinico-pathological features of extrarenal involvement, both during the acute phase and later.

The pathogenesis of multiorgan damage may be secondary to TMA, to a direct action of bacterial toxins at the cellular level and eventually to other complications such as coagulopathy, metabolic derangements, anoxia, over-infection, etc. Extrarenal TMA manifests as endothelial damage and thrombosis in small arteries, arterioles and capillaries, with oedema, haemorrhage and necrosis in adjacent tissues, without cellular infiltration. Clinical and pathological observations suggest a direct relationship between the severity of colonic involvement and renal TMA, both being clearly associated with the intensity and extent of extrarenal involvement.

The present discussion is based on our former experience with a very large series of Argentinian cases of classic HUS [5, 6]. A mean of 250–300 new cases have been diagnosed annually in our country since the late 1960s. Autopsies were performed, at different times in the acute stage, in 64 patients, most of whom belong to the early years of our study. Clinical and follow-up data of the survivors, together with a review of the available literature are included in this paper. The mortality of HUS has decreased to less than 3% in most paediatric Argentinian centres; this decreases the number of available autopsies, but increases the opportunities for studying sequelae. Although many isolated autopsies have been reported, the pathology of HUS has been studied in several groups of patients [7–9].

Gastrointestinal tract

Lesions of the gastrointestinal tract were found in 29 of our autopsies, all performed during the first 2 weeks of illness. They were always present in the large bowel, with areas of haemorrhagic necrosis and ulceration. On microscopic examination TMA was always more extensive in the mucosa and submucosa, although usually the entire thickness of colonic wall was affected, at least focally. Perforation and peritonitis were seen in 6 patients who required colectomy.

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Colonic damage was accompanied by similar lesions in the small bowel in 5 infants, stomach in 1 and oesophagus in 2.

Acute non-dehydrating diarrhoea is present in every patient, but in 80% the stools are bloody, sometimes massively so; blood is red and mixed with mucus, although melena may also be observed. Intense colicky abdominal pain and profuse vomiting are often present, as well as moderate abdominal distension and tenderness [10–12]. Rectal prolapse is found in 8% of patients [13]. These symptoms precede oligoanuria and persist for some days thereafter. They are more prolonged and serious in some cases, heralding complications such as massive intramural haematomas, intussusception, gangrene or perforation. They worsen prognosis, make peritoneal dialysis difficult, and occasionally require surgery, with a high post-operative mortality. Six of our autopsy cases had required colonic resection.

Although intussusception may be wrongly diagnosed because of a combination of pallor, pain and bloody stools, it often occurs in HUS in our experience. Four exceptional patients evacuated segments of gangrenous bowel after long-standing intussusception, with consequent severe stricture in 3. Secondary stenosis of the left colon may occur even after less severe haemorrhagic colitis, and the same can happen occasionally in the small bowel or oesophagus [14]. In non-endemic areas, HUS haemorrhagic colitis may be wrongly diagnosed as ulcerative or pseudomembranous colitis, polyposis, shigellosis, etc., requiring eventual X ray evaluation, endoscopy and even biopsy [15–17].

Pancreas, liver and salivary glands

Pancreatic lesions were present in 19 of our autopsies. They consisted of TMA, restricted to the islands of Langerhans in 17 cases, 4 with slight necrosis of adjacent tissues. Two children had massive haemorrhagic necrosis of the pancreas, which contributed to their death. Similar findings have been described by other authors, including late calcification and exocrine pancreatic insufficiency [18]. Transient glucose intolerance manifested as severe hyperglycaemia, during peritoneal dialysis, was found in 5 of our patients; permanent insulin-dependent diabetes is present in only 2 more than 2 years after HUS; few similar cases have been reported [19]. There is no clear explanation for the selectivity of the damage to insular tissue.

Liver compromise in HUS is difficult to evaluate, because many liver functions may be modified by anaemia, cardiac failure, poor caloric intake, coagulopathy, complicating infections, etc. Nevertheless [20] significant increases in serum levels of hepatic enzymes and hepatomegaly have been ascribed to liver involvement. In only 1 of our autopsies a few thrombi were found in the hepatic sinusoids. Salivary gland involvement has been reported only once [21] and was not found in our patients.

Cardiovascular system

Electrocardiographic evidence of ischaemia is found quite often in the acute phase and may be related either to TMA or to anaemia, fluid overload, electrolyte imbalance, side effects of drugs, malnutrition, etc. Accelerated hypertension may produce left ventricular hypertrophy and/or dilatation, with relative ischaemia and myocardial necrosis. We have not detected permanent myocardial sequelae, although they may have been overlooked, as suggested by a report of dilated cardiomyopathy [22].

The most frequent heart lesions in our autopsies were those of TMA in small myocardial vessels, present in 15 patients; they were usually accompanied by spotty necrosis; only 2 had grossly visible areas of infarction in the left ventricular wall; 2 had multiple haemorrhages and another necrotic foci without TMA. Cardiac lesions were the main cause of death in 7 children. Myocardial TMA has been described in 1 of 3 and 2 of 9 autopsies in two other reports [7, 8].

Central nervous system

The brain was examined in 32 of our autopsies. Lesions of TMA were found in 11 cases; their distribution was random throughout the whole encephalon, but in 8 they were present in the choroid plexuses. Intracranial haemorrhages were seen in 21 autopsies: 5 patients had large subdural haematomas and 16 had parenchymal haemorrhages, ranging from extensive petechiae in most cases to haemorrhagic infarctions in 2 patients. Less specific changes were also found: cerebral oedema in 16, focal necroses, spongiosis and gliosis in 9 cases. The central nervous system injury was the main cause of death (either the single cause or associated with another) in 12 of the 32 complete autopsies, and in 5 in whom the brain was not examined.

Minor neurological symptoms, such as irritability, somnolence, myoclonic jerkes, tremor or ataxia, are present in 90% of patients. Severe manifestations are also often found, such as convulsions in 30% of patients, status epilepticus in 3%, coma in 15%, focal motor deficits in 6% and decerebrate rigidity in 4%. All have been less frequent in our recent experience, possibly due to improvement in the control of renal failure and of the metabolic and haematological derangements. Of particular interest was the finding of papilloedema and/or retinal haemorrhages in 68% of the fatal cases; they were always associated with the most severe and progressive symptoms of brain dysfunction [23].

Significant neurological sequelae, such as developmental retardation, focal motor deficits, cortical blindness and recurrent convulsions [3, 5, 6, 24], have been observed on prolonged follow-up. Many patients with residual symptoms in the first months or years of follow-up completely recover or have only minor sequelae in the areas of behaviour, verbal intelligence, reading comprehension and vocabulary [25]. We have not demonstrated occlusion of the main cerebral arteries, as reported by others [26, 27]. Many studies of patients with severe residual damage have shown computed tomographic scan and magnetic nuclear resonance images compatible with focal atrophy of the brain and porencephalic cysts.

Other organs

In our autopsies we found occasional lesions of TMA at other sites (adrenals in 5 cases, spleen in 3, lymph nodes and urinary bladder 1 each), with no relation to the clinical course of the patient. Microthrombi were present in the lungs in 5 autopsies. All these patients had clinico-pathological evidence of terminal sepsis; pulmonary changes due to infection were also found.

The very high catabolic rate of infants with HUS and the rapid decrease in their muscular mass suggest the possibility of ischaemic muscular injury. One report showed very high total creatine kinase (CK) and CK-MM serum levels during the first days of HUS, with normalisation within a few weeks [28]. A recent paper describes rhabdomyolysis in a patient, with lesions of TMA in the muscle biopsy [29].

Final remarks

Although haemorrhagic colitis precedes anaemia and oliguria, symptoms of extrarenal TMA coincide with and modulate the prognosis of the acute phase. In some gravely ill infants, secondary falls in erythrocytes and platelets are accompanied by aggravation of extrarenal involvement. It is reasonable to assume that the circulating verotoxin originating from the bowel causes vascular injury when endothelial cells have specific receptors for the toxin. Future research to clarify the pathogenesis of TMA in classic HUS may contribute to the prevention and treatment of the basic lesion of this systemic disease.

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