be selected. Furthermore, in view of the recent use of haploidentical donors in stem cells transplantation [11], it would be important to evaluate if a similar effect is observed in this type of treatment for which patients often lack an HLA identical donor. Likewise, implementation of cadaver kidney transplantation programme with such acceptable mismatches could also be envisaged.

References


Haemolytic–uraemic syndrome—the experience in Argentina

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Introduction

Haemolytic–uraemic syndrome (HUS) was first described and given its name by Swiss haematologists [1]. The first observations on children, most of whom had reversible acute renal failure, came from Argentina [2]. Subsequent experience showed that the incidence of this type of thrombotic microangiopathy (TMA) was higher in Argentina than in any other part of the world. Up to 1993, >5500 cases have been registered in Argentina, the incidence being 2.9/100 000 children, of <15 years of age (Nephrology Committee of the Argentine Society of Pediatrics), and these numbers may even be an underestimate.

Epidemiology

The clinical experience in Argentina had shown that >90% of the patients had a diarrhoeal prodrome which was bloody in 76% of cases [3]. Subsequently it was confirmed that these were due to verotoxin-producing Escherichia coli [4]. The proportion of gas-

troenteritis associated with Shiga toxin is ~23% in Argentina, much higher than the 0.6–2.4% reported from other parts of the world.

Clinical aspects

The prevailing form of the disease in Argentina is the epidemic form, caused by the cytotoxin which is produced by certain strains of E. coli. Several treatment trials have been carried out in the acute stage of this form of HUS; three prospective and controlled studies were executed in children with the diarrhoeal form of HUS. One was performed at a time when intravascular coagulation was believed to be responsible for HUS [5]. The authors compared heparin against supportive treatment and found no benefit, while the frequency of intracranial haemorrhage was increased. Two later studies [6,7] were designed to validate reports on the beneficial effect of plasma infusion or plasmapheresis in the atypical form of HUS. In the controlled studies, however, patients treated with plasma infusion for 2 or 3 weeks had similar early and late outcomes to those of matched controls. Obviously, efforts to prevent the intestinal infection or the effect of the toxin must take priority if the burden from the disease is to be relieved.
Treatment of the intestinal infection with antibacterial drugs is apparently harmful and increases the risk of development of HUS [8], possibly because massive amounts of toxin are liberated from disintegrating bacteria.

Preventive measures

Three approaches may diminish the incidence of HUS. First, adequate information must be available to the public about the risk of consuming undercooked meat, unpasteurized cheese and raw milk. Investigators in Argentina noted that a high proportion of patients came from areas where unprocessed milk is usually consumed [9]. Violation of food hygiene also explains outbreaks in nursing homes or day-care centres.

A second approach might be prevention through development of vaccines directed against *E. coli* or its toxins. Efforts in this direction are underway in some countries with a high prevalence of toxigenic *E. coli*.

A third approach is currently under study in Argentina, i.e. administration of orally administered toxin-binding absorbents [10].

Evolution and sequelae

In Argentina, recovery from acute renal failure is seen in >95% of children with the epidemic form of HUS. Haematological changes are seen only in the acute phase, and sequelae involving the central nervous system (CNS), pancreas, colon or other organs are infrequent. Chronic renal disease, on the other hand, is seen in 35–60% of affected children [11].

When large cohorts are followed for more than 1 year after the acute stage, three different outcomes are seen. Spizzirri et al. [12] observed 118 children who had HUS in early childhood after >10 years of follow-up. The first group of 63% had normal urine analysis and creatinine clearance, a second group of 18% had persistent proteinuria with normal creatinine clearance, and a third group of 19% had different degrees of decreased glomerular filtration, generally associated with proteinuria and hypertension.

After recovery from the acute renal failure, patients may progress to terminal renal failure within 2–5 years, either without having recovered normal Ccr or, in the majority of patients, after having recovered normal serum creatinine levels or creatinine clearance, but exhibiting persistent proteinuria. This latter group arrive in terminal renal failure after an average of 10 years [13], but occasionally even after >20 years.

Several findings in the acute stage are predictors of late renal prognosis. These are the presence and duration of anuria, hypertension persisting after correction of hypervolaemia and severe involvement of the CNS or intestine. These signs are indices of severe and widespread initial microangiopathy.

**Mechanism of progression**

Epidemic HUS constitutes a clinical model of one-shot disease, i.e. acute reduction of the number of functioning nephrons with subsequent progression to chronic renal failure by intrinsic mechanisms, depending on the number of nephrons lost. There are three lines of evidence to support this hypothesis. First, the histological lesion in the chronic stage resembles those found in experimental and clinical models of hyperfunction of residual nephrons, i.e. focal and segmental glomerulosclerosis with mesangial expansion and focal tubular atrophy and interstitial scarring [14].

Second, there is a maladaptive increase of glomerular filtration rate (GFR). For example, we studied 12 children with normal Ccr who had had HUS many years previously [15]. Four of the 12 were unable to increase inulin clearance after an acute protein load. Peak inulin clearance values after a protein load in the 12 patients were significantly lower than in normal children (84.9 vs 155 ml/min/1.73 m², *P*<0.025). Third, there is a deficit of glomerular permselectivity. Some children who had completely normal clinical and laboratory findings years after the acute episode of HUS developed microalbuminuria [16], possibly a reflection of hyperfiltration in residual nephrons with increased filtration of macromolecules.

These considerations are important in the development of strategies to halt the late progressive decrease in renal function. Prospective studies currently are underway to evaluate the effectiveness of restriction of dietary protein intake and of the use of angiotensin-converting enzyme inhibitors. One question which remains to be answered is: which is the appropriate time to introduce these measures? Starting treatment once microalbuminuria appears may increase the chances of interfering successfully with progression.

**Transplantation**

The registry of the Argentine Society of Pediatrics reveals a prevalence of 16% of HUS among the 178 children entered into chronic renal failure, dialysis or transplantation programmes in 1996. HUS accounts for end-stage renal failure in ~20% of children requiring renal transplantation in our centre [17].

The first report of successful transplantation for HUS was published in 1972 by Cerilli [18], and later many centres confirmed the absence of recurrence of the disease in the graft, including in the substantial number of children with the epidemic diarrheal form transplanted in Argentina. This was contradicted by one report from Minneapolis [19]. To resolve this controversy, we reviewed the long-term course of 19 renal grafts in children with the ‘classic’ epidemic type with a mean follow-up of 5 years with a range of 1–11 years [20]. Survival of the grafts, maintenance of stable renal function, incidence of acute rejection and prevalence of proteinuria and hypertension was not different from those of a randomly selected control group of...
children transplanted for other diseases. No recur-
rences were observed and no evidence of thrombotic
microangiopathy was seen in the surgically removed
kneys or in renal biopsies. It is our opinion that in
the HUS associated with Shiga toxin, renal trans-
plantation is indicated and has a very low risk of
recurrence. Graft outcomes are not different from
those seen in other diseases. Cyclosporin is known to
increase the risk of recurrent or de novo thrombotic
microangiopathy. It is therefore of interest that 12 of
the 19 children in our series received cyclosporin
in their immunosuppressive protocol. No thrombotic
microangiopathy was observed.

These findings subsequently have been confirmed by
a follow-up report from Minneapolis [21] and a large
French–German collaborative study. They found no
recurrences in HUS associated with diarrhoea, but a
substantial risk in the atypical sporadic or familial
forms.

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The diagnostic trash bin of focal and segmental glomerulosclerosis—an effort to provide rational clinical guidelines

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In the age of evidence-based medicine, physicians are
facing the task of integrating their individual clinical
expertise and the best external evidence. To meet these
goals for the treatment of a patient with proteinuria,
normal renal function and the histological diagnosis of
focal and segmental glomerulosclerosis (FSGS)
turns out to be rather difficult, as the published evi-
dence, concerning the efficacy of immunosuppressive
therapy, is extremely confusing. The chance of
obtaining complete remission by steroid therapy has

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