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Fulminant hepatic failure in childhood

Acute liver failure is uncommon in infants and children. Nevertheless, it still carries a high mortality; hence intensive treatment is justified, since most survivors have essentially normal liver function after recovery. Psacharopoulos *et al*[1] have recently reviewed the treatment at King's College Hospital in London between 1969 and 1977 of 31 children with fulminant liver failure, of whom nine survived.

The clinical picture is one of jaundice and encephalopathy developing within eight weeks of the onset of features of liver disease (and usually very much earlier). Most of the cases in the King's series occurred after an apparent attack of acute hepatitis (all HBsAg-negative); other, rarer causes were poisoning by paracetamol and *Amanita phalloides* and reactions to halothane anaesthesia. Encephalopathy preceded the jaundice in some of the children with paracetamol poisoning but usually jaundice was the first sign of liver disease.

The wide range of metabolic functions subserved by the liver necessarily makes the clinical course of hepatic failure complex. In some patients the encephalopathy is rapidly progressive. The coma is conventionally classified from stage I (minor disturbances of consciousness) to stage IV (deep coma unresponsive to painful stimuli). Few patients who reach stage IV coma are likely to survive, and only one of the 19 in the present series lived. Acute cerebral oedema occurs in about half the fatal cases (though papilloedema is seldom seen). Liver function values are grossly disturbed. The serum bilirubin concentration and aminotransferase activities are usually high, and the prothrombin time appreciably prolonged. The prothrombin time is a good index of the degree of liver damage[2]: thus all children in the King's study with a prothrombin time prolonged beyond 90 seconds died.

Bleeding is a serious complication of liver disease, and in children with fulminant hepatic failure major gastrointestinal bleeding is particularly ominous. Whenever it occurred the child's condition deteriorated, and no child with bleeding problems survived. Among the many metabolic disturbances are lowered concentrations of sugar and potassium in blood and serum.[3] The concentration of sodium may fall in association with inappropriate water retention or rise with an overload of intravenous fluids. Either acidosis or alkalosis may result from a combination of antagonistic effects on acid-base balance. Renal failure and severe infection are further complications, the first related possibly to endotoxaemia[4] and the second to impaired host defence in liver failure.[5]

The management of liver failure demands the facilities of an intensive care unit and depends on maintaining the patient and supporting vital functions until hepatic regeneration can occur. More active treatment aimed at preventing further liver cell necrosis and stimulating growth of new liver cells remains only a theoretical possibility.

Absorption of nitrogen from the gut should be kept to a minimum by the use of enemas to empty the colon, lactulose to promote an acid environment limiting absorption of ammonia and toxic bases, and neomycin to reduce bacterial production of toxins within the gut. Feeding by mouth is stopped and blood sugar concentrations are maintained with intravenous fluids. Care must be taken with electrolyte balance, since both potassium depletion and (iatrogenic) sodium overload may easily occur. Infection and renal failure should be watched for and treated early. Cerebral oedema is an important cause of death. Fluid restriction, mannitol infusions, and dexamethasone have all been used, singly or in combination, with little effect on its incidence.

In another hepatic encephalopathy of childhood, Reye's syndrome, management has become more rational since the introduction of intracranial pressure monitors,[6] and their use would probably help treatment in all forms of fulminant hepatic failure. The control of bleeding depends on administration of fresh plasma, platelets, and coagulation-factor concentrates. In adults cimetidine has been claimed to be of value in limiting gastrointestinal bleeding,[7] but Psacharopoulos *et al*[1] could not obtain any evidence of its value in children. Nor are systemic steroids of value in limiting liver cell necrosis; indeed, they may worsen the prognosis.[8] A few children have been treated with either charcoal haemoperfusion or with haemodialysis using polyacrylonitrile membranes, but there is not enough evidence to recommend either form of treatment. Results with haemodialysis, however, appear encouraging, though treatment must be started before the onset of grade IV coma.[9] A final experimental treatment is perfusion of the patient's blood through living tissue, either human or animal; again there is little evidence that overall survival is improved.[10]

How much age influences the chances of recovery from fulminant hepatic failure is uncertain. In one study children had a much better prognosis than older patients, achieving a 34% survival[11] (compared with only 5% of patients over the age of 45). In contrast, the King's study[1] found no difference in the results in adults and children treated in the same unit.

Those children who survive this massive insult, however, seem to make a complete clinical recovery. All survivors were leading a normal life within four weeks of discharge from hospital. Nevertheless, liver biopsy specimens from most survivors in the King's study showed appreciable inflammatory change, sufficient to warrant a histological diagnosis of chronic aggressive hepatitis. Subsequent repeat specimens showed postnecrotic scarring. Adult survivors normally show rapid and complete histological recovery.[12]

Clearly children with such a severe and complex disease should be managed in specialised units. Only in this way will survival be improved in this potentially treatable disease. Transfer of very sick patients over large distances may be a problem; they should be accompanied by a doctor and a nurse, and on the journey intravenous fluids should be carefully controlled, giving high concentrations of glucose to prevent hypoglycaemia and limiting excessive sodium and water intake.

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The prognosis of multiple sclerosis

Multiple sclerosis is the most common neurological disease affecting young adults in temperate climates.[1] Despite the tremendous variability of its symptoms, clinicians naturally try to give their patients guidance on their prospects for continued employment and independence, the need for family and community support, and the eventual course of the disease. A truly prospective study applied to such a diverse disorder is seldom feasible[2]; and to be of value retrospective data need to adhere to strict criteria, conforming where possible with earlier studies. In particular, the retrospective approach carries a risk that milder cases may be overlooked. Case reports need to be eliminated where the information is sparse, and recent and more refined diagnostic methods such as visual evoked potentials may not have been used. Moreover, whatever the diagnostic approach, epidemiological studies need to take account of the clinically silent cases that may be discovered at necropsy.[3 4]

McAlpine's classic review[2] has now been reinforced by a computer-processed analysis of 349 patients collected from 1957 to 1976 and followed up for an average of nine years at the neurological centre in Lyon.[5] The main lesson of these actuarial data is that multiple sclerosis may be regarded as a single entity. Around 70% of patients who develop the disease do so between 20 and 40 years of age. Typically, the onset is at 30 with complete remissions; by the age of 34 the remissions begin to leave residual disability, and at 38 years the progressive phase sets in. These are mean ages and the standard deviation is 10 years. In the Lyon series 18% of patients showed progressive deterioration from onset.

Where early remissions are succeeded by a progressive phase the shorter the interval between the first two relapses the sooner the progressive phase appears. In the period before the progressive phase begins the frequency of relapses and the proportion of the relapses affecting the sensory and motor tracts and cerebellar system tend to increase while the proportion affecting the cranial and optic nerves decreases. At one time[2] sensory symptoms and symptoms relating to the cranial nerves and visual pathways were thought to remit more readily and carry a more favourable prognosis than motor or cerebellar symptoms, but Confavreux *et al*[5] conclude that the relative risks of producing lasting sequelae or triggering the progressive phase depend anatomically on the space occupied by these systems in the neuraxis.

Of the 349 patients in the French study, 140 were men and 209 women.[5] The men had a lower mean age of onset, but other studies have shown an opposite trend[6 7]—and the sex of the patient has no prognostic value. The sample proved too small for prognostic analysis of histocompatibility antigens, and no correlation was found between the cell count or total protein concentration in the cerebrospinal fluid and the eventual outcome. Increases in gammaglobulin concentration and in the ratio of gammaglobulin to total protein seemed to be more closely related to the age distribution of the patients than to prognosis.

The degree of disability was assessed on the McAlpine scale[2] as: no disability (grades 0-1), moderate disability (still ambulatory, grades 2-3), and severe disability (non-ambulatory, grades 4-6). There was a strong correlation of the age of onset with the interval to moderate disability: this interval averaged eight years in the youngest patients with age of onset at 20 but only one year in patients aged 50 at onset. Severe disability developed after 14·3 years in the young and after 4·8 years in the older patients. Ten per cent died within 15 years, and this suggests a mean survival time of around 30 years.

The disability score and duration of the disease were combined to define various forms of the disease. Patients with benign forms[6 8] (constituting 14% of all patients) show no disability after 10 years and moderate disability after 15 years. Whereas McAlpine[6] found a low relapse rate in the second year, Confavreux *et al*[5] commented that the number of relapses in the remittent phase had an interesting relation to outcome, the "benign" forms having a greater number of relapses. In contrast, patients with the "hyperacute" form (8% of the total) were severely disabled within less than five years. Hyperacute forms were three times more common in