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Reye's Syndrome

A clinician presented with a child, previously well, who has developed convulsions or disturbances of consciousness or both proceeding rapidly to coma is faced with a bewildering range of differential diagnoses. Head injuries, vascular accidents, intracranial space-occupying lesions, and direct infection of the central nervous system must be excluded on the basis of the clinical features and by appropriate investigations. Exogenous toxins may need to be looked for as well as metabolic disorders such as hypernatraemia, hypoglycaemia, diabetic acidosis, hypocalcaemia, hypomagnesaemia, uraemia, water intoxication, and acute porphyria. Hypertensive encephalopathy occurring early in glomerulonephritis before a renal lesion is suspected may also cause confusion. Also to be considered is acute toxic encephalopathy, a poorly understood condition in which convulsions and coma with fever and vomiting develop during such illness as upper respiratory tract infections, gastroenteritis, dysentery, pneumonia, or one of the exanthemata. Only supportive and symptomatic treatment is available for this condition.

With such a range of differential diagnoses, it is disappointing but understandable that another well-recognized cause of coma and convulsions in this age group, Reye's syndrome or encephalopathy with fatty degeneration of the viscera, is often not recognized in life[1] 12 years after Reye, Morgan, and Baral[2] first drew attention to it. Classically there may be a history of a mild prodromal illness from which the child is apparently recovering.[3-5] Vomiting, which may be severe, may precede central nervous system symptoms by 3-72 hours, but it does not occur in all cases. The common course is rapid progressive deterioration of consciousness, with convulsions proceeding to coma and decerebrate posturing, death often following in 24-48 hours. There are no focal central nervous system signs, nor meningismus. Papilloedema is unusual early in the course. Hyperpnoea or irregular respiration should arouse diagnostic suspicion. Mild to moderate hepatomegaly may indicate visceral lesions, but it is absent in more than half of cases. Jaundice is unusual.

Only by doing liver function tests is the diagnosis likely to be suspected in life. If two of the following criteria are satisfied without any other obvious explanation for the clinical and biochemical features, Reye's syndrome is a probable diagnosis: aspartate aminotransferase level more than two and a half times normal, a prothrombin activity of less than 60% of normal, and a blood sugar of less than 3 mmol/l or a C.S.F. glucose of less than 2 mmol/l. A blood ammonia level higher than 0·1 μmol/l further supports the diagnosis,[6] but hyperammonaemia may be transient. Raised serum levels of alanine, lysine, and glutamine and a low citrulline are the typical amino-acid pattern.[7] Confirmation of the diagnosis requires liver biopsy, but this is frequently ruled out by the prolonged prothrombin time. There is variable but often intense fatty infiltration of the liver, with diffuse vacuolation of the hepatocytes without nuclear displacement and no hepatocellular necrosis.[8]

Since the diagnosis of Reye's syndrome is difficult its incidence may be higher than is generally realized. About 40% of children diagnosed in life die.[9] Features associated with poor prognosis include a blood ammonia level higher than 200 μmol/l, a rapid progression to deep coma, a prothrombin time prolonged more than twice normal, increased intracranial pressure,[10] and electroencephalographic abnormalities.[11]

The aetiology and pathophysiology remain poorly understood. Some evidence links a variety of this syndrome in Thailand with aflatoxin ingestion.[12] A viral aetiology has been suggested owing to the recovery of viruses from the nasopharynx and faeces in individual cases and on epidemiological grounds,[13] but there is no direct viral invasion of liver or brain. The apparent concentration of 13 cases in one part of Canada which had been sprayed heavily with insecticide was followed by an experimental study in mice, in which pathological features similar to those in Reye's syndrome were produced by a virus in those previously exposed to insecticides. Neither the insecticides individually or in combination nor the virus caused similar pathological features.[14] Even the cause of the encephalopathy remains undetermined.

For the time being the treatment of Reye's syndrome remains supportive and empirical—namely, the correction of hypoglycaemia, electrolyte abnormalities, acidosis, and hypoxia. Artificial ventilation may be required. A reduced fluid intake—10% dextrose with maintenance electrolytes—is advised initially to minimize the risk of cerebral oedema, but this may have to be modified if the patient is dehydrated or if inappropriate release of antidiuretic hormone occurs. Neomycin by nasogastric tube and laxatives and enemata to minimize ammonia reabsorption from the gut seem rational treatment, but they are not of proved value,[17] nor is dexamethasone or mannitol, the usual treatment for increased intracranial pressure.[10] The bleeding diathesis may require correction with fresh frozen plasma or whole blood. The apparent beneficial effects of peritoneal dialysis[18] and exchange transfusion[17] have not been confirmed in some subsequent studies.[10 19] Potentially hazardous recommendations that have been associated with recovery include glucose and insulin,[20] L-citrulline,[15 16 21] and nicotinic acid.[22] All must be considered of unproved value. No data are available on optimum calorie intake nor on how they should be provided.

The acute nature of this syndrome, its sporadic occurrence, and its variable severity caused difficulties in assessing the value of therapeutic regimens as well as in sorting out the pathophysiology, a necessary requisite for rational therapy. Co-operative studies may resolve these difficulties, but they will be successful only if Reye's syndrome is considered during life in all children with acute encephalopathy of unknown cause.

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The Several Viruses of Post-transfusion Hepatitis

The introduction of routine screening of donor blood for the hepatitis B surface antigen (HB_sAg) raised hopes for the eventual control of post-transfusion hepatitis. However, though reductions in frequency of up to 75% are possible,[1] cases of post-transfusion hepatitis still occur. In some instances HB_sAg may be found in the serum even when the transfused blood had been passed as free of antigen by the most sensitive techniques currently available—passive haemagglutination[2] and radioimmunoassay.[3] In most such cases, however, tests for HB_sAg are negative, and the absence of an antibody response either to the surface or to the core antigen means that the hepatitis B virus is extremely unlikely to have been responsible.[4 5] This has highlighted the question of what the cause of the hepatitis is in these circumstances.

One obvious candidate is the hepatitis A virus; but, while the incubation period in some cases of post-transfusion hepatitis is short,[2] in many cases it has been longer than the six-week limit generally accepted[2 1] for infection with the A virus. Recently, Feinstone *et al.*[5] have examined directly the role of this virus in 22 patients with HB_sAg-negative post-transfusion hepatitis using immune electron microscopy to detect antibodies to the faecal particles currently thought to represent the A virus. They found that sera from 13 of the cases were positive for such antibodies before developing acute hepatitis and that the titre did not subsequently increase, while sera in the other nine patients were negative throughout. Furthermore, the incubation period in more than half the patients was greater than six weeks.[5] These findings, together with the known predilection of the A virus for transmission by the faecal-oral route, make it clear that it cannot be a common cause of HB_sAg-negative post-transfusion hepatitis.

Other possibilities that must be considered are the herpes viruses, which include herpes simplex, the Epstein-Barr virus, and cytomegalovirus. Herpes simplex hepatitis usually occurs in newborn or young children, and has been reviewed recently in these columns.[6] The Epstein-Barr virus may be carried in latent form in the circulating leucocytes of healthy persons, and may occasionally be transmitted by blood transfusion.[7] However, 80-90% of individuals will have acquired antibody to this virus by adulthood, and it can therefore be only a very infrequent cause of post-transfusion hepatitis. In contrast, cytomegalovirus does appear to account for a small number of cases,[7] and since only about half the general population possess antibodies seroconversion is much easier to observe than with the Epstein-Barr virus. There are, however, a number of problems. Firstly, seroconversion does not necessarily prove infection, since it is also observed in equal or greater frequency after transfusion both in patients who subsequently develop typical HB_sAg-positive hepatitis due to the B virus and in those who never contract acute hepatitis.[4 8] Secondly, it is still uncertain in the cases that show seroconversion whether the disease is transmitted de novo or reflects merely a reactivation of pre-existing infection—though the observation that the frequency of seroconversion increases with the number of units transfused and that the antibody is often of IgM class favours a primary infection.[8] Finally, the incubation period of cytomegalovirus is about 2-4 weeks, much shorter than that observed in most cases of hepatitis after transfusion. Thus the exact role of cytomegalovirus in post-transfusion hepatitis remains uncertain.[4 5 8] These considerations have led Prince *et al.* to suggest that HB_sAg-negative cases with a long incubation period may be due to another as yet unidentified hepatitis virus—so-called type C.[4]

The management of post-transfusion hepatitis, once the diagnosis has been made from other causes of postoperative jaundice such as halothane hypersensitivity, benign intrahepatic cholestasis, and mechanical obstruction of the intrahepatic biliary tree, is less of a problem. Simple supportive therapy with adequate fluid and glucose intake and standard precautions against infection are usually all that are necessary. However, a close watch should be kept for confusion and drowsiness, the warning signs of encephalopathy, which are indicative of a fulminant course with high mortality and requiring more intensive therapy. Occasionally, abnormalities of biochemical liver function may persist for some months after apparent clinical recovery. This is particularly apt to occur in patients with persistent HB_s antigenaemia, and further investigation by liver biopsy is essential to identify patients in whom progression to chronic hepatitis is occurring and who require immunosuppressive therapy.

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High Altitude Retinal Haemorrhage

Exposure to high altitudes carries a number of health hazards, the most recently described of which is retinal haemorrhage.

The condition was first studied in 1969 by Frayser *et al.*[1] Among 25 persons examined in a laboratory at 17 500 ft (5330 m) 9 developed retinal haemorrhage. Of these, 8 had no symptoms; the ninth had headache and a scotoma, with papilloedema, very tortuous retinal vessels, and a haemorrhage at the macula. Schumacher and Petajan[2] gave details of findings in 39 subjects who spent up to 24 days at or above 14 200 ft (4330 m) on Mt. McKinley. Fourteen of the party had retinal haemorrhage, the condition being commoner in those who were prone to vascular headache, who developed altitude headache, and who ascended rapidly above 14 000 ft (4200 m). Of note was the finding of retinal haemorrhages in six of nine climbers who made "quick dashes" to the summit from 10 000 ft (3000 m). Among 1925 people with acute mountain sickness Singh *et al.*[3] found engorgement of the retinal veins in 17, papilloedema in 4, and vitreous haemorrhage in 3. In 34