Encephalopathy and fatty degeneration of viscera

Reye's syndrome

Encephalopathy and fatty degeneration of the viscera were reported as early as 1929 (Brain, Hunter, and Turnbull), but it is only in the past 10 years that the clinical and pathological features have been clearly defined (Mann *et al.*, 1962; Reye, Morgan, and Baral, 1963; *Lancet*, 1969; Evans *et al.*, 1970; Guillete, Berlin, and Finkelstein, 1971). Considerable problems still exist regarding many aspects of the disorder. The aetiology remains unknown and the pathogenesis is poorly understood. The lack of striking clinical features of hepatic involvement may cause the disorder to be overlooked in life, but even if the diagnosis is made, there are considerable problems in management. The assessment of the relative efficacy of different forms of therapy is difficult, as it is not yet clear which of the many measurable parameters which may be abnormal in the syndrome are the best indices of prognosis. This is a major problem in a disorder which may follow a continuum of severity from the invariable fatal cases, such as those reported initially, to milder or even subclinical cases. There is considerable variation in the reported incidence in different areas. The incidence relative to the other acute encephalopathies in childhood is not clear. There has even been some debate as to whether the syndrome can be considered a specific entity. It may merely represent the effects of many different aetiological factors acting on the same metabolic pathway. The consistency of the reported findings do suggest, however, that the syndrome in childhood is a distinct pathological and metabolic response of sufficient homogeneity to be the basis of epidemiological and aetiological studies, and—if the diagnosis is made in life—for much needed investigations of pathogenic mechanisms and their response to therapy.

The pathological features are well characterized. There is marked cerebral oedema, with or without anoxic neuronal changes and neuronal degeneration, but with no cellular infiltration or demyelination. The liver at necropsy is swollen and tense, orange to pale yellow in colour, the cut surface being relatively bloodless, greasy, and firm. In liver biopsy specimens fatty infiltration is seen as diffuse small vacuoles most prominent in the periportal areas, but there is massive fatty infiltration in necropsy material. Liver glycogen is decreased. The nuclei of the hepatocytes may contain 1 to 4 irregular enlarged nucleoli but hepatocellular necrosis is not seen except in necropsy material. The portal tracts are normal. Electron microscopical examination of liver biopsy material (Partin, Schubert, and Partin, 1971) early in the course of the encephalopathy shows the hepatocytes to be universally affected by a process which results in swollen pleomorphic mitochondria, as well as small droplet triglyceride accumulation. There is also proliferation of smooth endoplasmic reticulum and a great increase in peroxisomes. The mitochondrial abnormalities gradually improve during clinical recovery. Fat deposition is seen also in the renal tubules and myocardium. Chromatographic analysis of lipids shows increase in both triglycerides and free fatty acids in liver extracts with only triglycerides increased in kidney extracts (Bourgeois *et al.*, 1971a).

While the clinical features are not pathognomonic, with a few readily available laboratory tests, the diagnosis can often be strongly suspected in life. The disorder is recognized in children aged 2 months to 15 years. The onset is typically acute with vomiting, disturbances of consciousness, convulsions, coma, and often decerebrate posture. There may be a history of a mild prodromal illness from which the child was apparently improving. Physical examination reveals a stuporose, agitated, hyperactive, comatose, or convulsing child, with no apparent cause. Hyperpnoea or irregular deep respirations are common and should suggest the diagnosis. There are no focal neurological signs and no evidence of meningeal irritation. Mild to moderate hepatomegaly is the only clinical suggestion of hepatic involvement, and even this is lacking in 50% of cases. The serum bilirubin level is normal or occasionally slightly increased,

but the prothrombin time is usually prolonged and the serum aspartate aminotransferase level is raised. Hypoglycaemia is common in children of less than 5 years, but is rarely found in older children. Hypoxia and acidosis are frequently found. CSF is normal except for its sugar content which may be low. Electroencephalography shows diffuse changes with slow wave activity predominating, but there is no specific abnormality. These features will often permit a presumptive diagnosis of Reye's syndrome, and histopathological confirmation by liver biopsy may be deferred until the coagulation abnormalities are corrected.

The clinical course is often of deepening coma and death. In the first 200 cases reported the mortality was 80% (Guillete et al., 1971), but more recent reports (see below) indicate a lower mortality of 25% to 70% perhaps because milder cases are diagnosed or management is better. Silverman, Roy, and Cozetto (1971) report that one-third of survivors had severe CNS sequelae such as mental impairment, seizures, or hemiplegia. Olson et al. (1971) and Huttenlocher (1972) found no significant residual effects in 21 and 8 children, respectively. Again, it is not clear whether these differences are due to different severity of disease or to better care.

The incidence of the syndrome is difficult to assess, varying from rare sporadic cases to being a leading cause of death in 1 to 6 year olds in Thailand (Olson et al., 1971). Cases appear to occur in minor outbreaks in a fairly wide area, usually without any recognized link between individual cases (Reynolds et al., 1972; Glick et al., 1970), though more than one case may rarely occur in a family (Thaler et al., 1970).

No known infectious or toxic agent or metabolic abnormality has been recognized which will consistently cause the clinical biochemical and histopathological lesions. Viral infection has been suggested on the basis of the recovery of viruses from a few patients, the frequency of varicella as the prodromal illness (Norman, 1968), and also because the incidence of the syndrome increased concurrently with outbreaks of influenza B infection in two epidemiological studies (Glick et al., 1970; Reynolds et al., 1972). Toxins that have been considered in the aetiology include salicylates (Norman, 1968; Reynolds et al., 1972), pteridines (Curry, Guttman, and Price, 1962), and isopropyl alcohol (Silverman et al., 1971), but the evidence is weak. More important perhaps are aflatoxins, mycotoxins produced by many species of aspergillus and penicillium. The hepatic effects of this group of toxins, hepatitis with bile duct proliferation or

hepatoma formation, are dose related and vary from species to species, with greatest hepatic sensitivity in the young (Wogan and Pong, 1970). Administration of aflatoxins to young female Macaque monkeys produces the clinical laboratory and histopathological features of Reye's syndrome, except that hepatic necrosis is marked and there is bile duct hyperplasia (Bourgeois et al., 1971b). In Thailand, Olson et al. (1971) have shown that the degree of aflatoxin contamination of foods follows the seasonal and geographical incidence of encephalopathy and fatty degeneration of the viscera. Chemical assay of the tissue of these patients shows higher concentrations of aflatoxins than are found in those that die of other disorders or in accidents. Yet family outbreaks are rare, though contaminated food is presumably shared. In part this may be attributable to the amount ingested or the increased sensitivity of the young. Another possibility is that aflatoxin alone will not produce the full syndrome but will do so in the presence of other unrecognized factors. Though this association has been well documented only in Thailand the fungi producing these mycotoxins are ubiquitous and may grow on many foods with maximum growth rates at 25 to 30 °C.

Reye's syndrome has many features in common with vomiting sickness of Jamaica (Stuart, 1970), a disorder which is said to be much less common since it was appreciated that it was caused by a hypoglycin from unripe ackee fruit (Tanaka, Isselbacher, and Shih, 1972).

The cause of the encephalopathy is undetermined. There is no evidence of primary CNS infection. A toxic factor acting directly on the brain as well as the liver has been suggested, but at present it seems more likely that the encephalopathy is secondary to metabolic effects of the hepatic lesion. Apart from lack of jaundice, many of the features are similar to acute fulminant hepatic failure. Hypoglycaemia is only one of the known metabolic lesions which could be instrumental in causing the encephalopathy. Ammonia retention, which if marked carries a bad prognosis, is also important, particularly since the nonesterified fatty acid concentration is also raised (Bourgeois et al., 1971a). This in itself can cause coma (Trauner et al., 1972; Walker et al., 1970). In a variety of experimental animals it has been shown that these two biochemical abnormalities have an additive effect in causing coma (Zieve et al., 1972). Abnormalities of many forms of intermediate metabolism already documented, such as raised pyruvate and lactate levels, may also contribute. If metabolic changes in hepatocytes mirror the ultrastructural changes, many other abnormalities

are likely, involving, for example, amino acid and catecholamine metabolism as has been found in hepatic encephalopathy (Williams, 1972).

Therapy is empirical and far from satisfactory. Hypoglycaemia, hypoxia, acidosis, and electrolyte abnormalities should be corrected in the conventional fashion. Assisted respiration may be necessary. The bleeding diathesis may require correction by infusion of fresh frozen plasma. A protein-free diet with sufficient carbohydrate intake to minimize endogenous protein catabolism, neomycin by nasogastric tube, and enemata as used in hepatic encephalopathy seem rational and are commonly used. Dexamethasone or mannitol infusions to minimize cerebral oedema are used but are of no proven value in this disorder. Peritoneal dialysis, which may remove hypothetical toxins and is useful in correcting refractory metabolic abnormalities, has been used in cases which have survived (Pross, Bradford, and Kreuger, 1970; Silverman *et al.*, 1971), as has exchange transfusion which has similar theoretical uses and also corrects bleeding disorders due to clotting factor deficiencies (Huttenlocher, 1972; Partin *et al.*, 1971). Both have their advocates and should be considered, but their effectiveness has still to be established in controlled trials. In spite of such measures, mortality remains high.

While it is reasonable to assume that early diagnosis and detailed documentation of biochemical abnormalities may lead to a better understanding of the pathogenesis and more rational therapy in this disorder, further studies in experimental animals or the considerable research in the management of acute hepatic failure may also provide useful information. For the moment, the most hopeful line of study appears to be a detailed epidemiological study of cases as they occur in any geographical area attempting to identify and thus avoid possible aetiological factors.

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