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Reye's syndrome: 20 years on

Reye's syndrome is an acute, rare, but serious disorder of childhood in which vomiting and coma develop three to four days after the onset of what appears to be a mild, unremarkable, viral illness. First highlighted 20 years ago,[1] its diagnosis and management still present many problems.[2] The cause remains unknown. The prime feature is a characteristic hepatic pathology,[3] with raised serum transaminase activities, a raised blood ammonia concentration, and a prolonged prothrombin time, indicating liver dysfunction, though there are usually no clinical features indicating liver disease. There are no focal neurological signs or features of meningeal irritation, the coma being associated with cerebral oedema without cellular infiltration or demyelination.

Reye's syndrome is not notifiable or reportable. A system of voluntary surveillance in parts of the United States has recorded over 2000 cases since 1968, which suggests an incidence of Reye's syndrome of from 0·37 up to two cases a year per 100 000 people of less than 18 years.[4] Great regional variations in incidence occur within the United States, with a preponderance of cases in rural or suburban areas.[5]

The incidence may be lower in Britain.[6 7] The mortality in reported cases in the United States has fallen from 80% to around 20%,[4 8] but 15% of children with mild symptoms still die.[2] Depending on the intensity of the investigations, permanent neurological or psychiatric disorders may be found in one third to two thirds of survivors.[9] The mortality and morbidity are highest in children of less than 12 months.[2]

The prodromal viral illness is usually a respiratory tract infection, with influenza B being particularly prominent in children of 10 to 11; in children aged 5 to 9 varicella is more common, while in even younger age groups the antecedent may be diarrhoea. In children up to 18 years the estimated incidence of Reye's syndrome is about one in every 2000 patients with influenza B[5] and one in every 4000 with chickenpox.[5 10]

The initial feature that should lead to consideration of the diagnosis is profuse and persistent vomiting. This is associated with or rapidly followed by a change in the child's mental state; quiet, withdrawn, or irrational behaviour and clumsy movements may progress to delirium, convulsions, and coma. Medullary coning and brain death may occur in severe cases between four and 60 hours after onset; or the neurological state may stabilise or improve at any stage short of brain death and the child may recover.[11] Infants with Reye's syndrome typically present with tachypnoea, respiratory distress, hyperventilation, seizures, and apnoea. They have enlargement of the liver more often than older children.[12] The patient is usually afebrile with no clinical features of liver disease.

If either the serum transaminase activity or blood ammonia concentration is measured the results are likely to be more than three times the upper limit of normal. The prothrombin time is frequently prolonged. Hypoglycaemia is a feature only in patients who are severely ill, and particularly in those aged less than 2 years. When the cerebrospinal fluid is examined it is found to be normal apart from the sugar content being low in some instances.

A wide differential diagnosis has to be considered in patients with vomiting, coma, and raised serum transaminase activities.[2] In infants the most important possibilities are inherited metabolic disorders, particularly urea cycle defects, systemic carnitine deficiency, glutaric acidaemia, fructosaemia, and organic acidurias. The diagnosis must also be considered in what seems to be "near miss" sudden infant death syndrome. In all age groups the differential diagnosis must also include hypoxic liver and brain damage, shock associated with severe bacterial infections or endotoxaemia, and the effects of dehydration. Severe generalised viral infections such as varicella and adenovirus infections may cause liver damage as well as encephalopathy.[13]

Any encephalopathy which produces convulsions requiring intramuscular injections may raise transaminase activities. Glycogen storage disease and insulin producing tumours may occasionally cause diagnostic difficulties. Rarely, fulminant hepatitis may cause confusion before the onset of jaundice. Finally, a wide range of toxins and drugs either in overdose or as idiosyncratic reactions may mimic this syndrome.

Percutaneous liver biopsy is an essential investigation in supporting the diagnosis of Reye's syndrome.[3 11 14] Not only will this provide the histological, enzymatic, and ultrastructural features confirming the diagnosis: it may also provide essential tissue for excluding inborn errors of metabolism. Unfortunately, a severe coagulation defect may preclude liver biopsy in the acute stages. On gross examination the biopsy specimen may appear yellow or white. Frozen sections or sections fixed in Bouin's solution and stained for fat will show a panlobular distribution of small fat droplets in every liver cell. Only when these fat droplets coalesce are they large enough to appear as holes in material embedded in paraffin stained with haematoxylin and eosin. Hepatic necrosis and inflammation are absent or inconspicuous. The lipid may clear in two to five days in mild cases but may persist for up to nine

days. Within one month the liver returns to normal. Histochemical stains on days 1 to 6 may show severe reduction of mitochondrial enzymes such as succinic dehydrogenase and cytochrome oxidase. Electronmicroscopical examination shows four main features: loss of glycogen, accumulation of lipid, an increase in peroxisomes, and a characteristic swelling of mitochondria, which in addition become pleomorphic with fragmented cristas and flocculation of intrametrical protein.

Reye's syndrome is currently thought to be an acute, apparently self limiting derangement of hepatic mitochondria with both structural changes and impairment of many aspects of their function. Similar mitochondrial structural changes may occur in muscle and brain.[15] The mitochondrial lesion is presumed to stem from a viral host interaction perhaps dependent on the host genetic make up and possibly modified by exogenous factors.[14] Of these, salicylates remain the focus of public interest[16] because the original interpretation[16–19] of three case-control studies[20–22] has been challenged[23–25] after re-examination of the original data[25 26] by independent institutes commissioned by the drug industry. In the original case-control studies drug histories obtained in hospital from 137 patients with Reye's syndrome (of whom only in 20% was the diagnosis confirmed by biopsy) were compared with those obtained from 247 children from the same areas who had presumed viral illnesses at the same time as the patients. These latter children were not admitted to hospital, and their histories were taken at home some weeks later.

None of these studies have been claimed to show a causal relation between salicylates and Reye's syndrome but have suggested a possible implication or a possible aggravation. The controversy has been fuelled by misinformation about salicylate concentrations in Reye's syndrome arising from measuring salicylates with methods which give spuriously high values in the presence of the metabolic abnormalities which occur in the syndrome[27 28] and a reported but superficial resemblance between the hepatic lesions in the syndrome and in deaths related to salicylate.[29] Salicylates undoubtedly cause an asymptomatic rise in serum transaminase activities in patients with rheumatoid arthritis,[30] but the mode of death in salicylate poisoning is complex and is not clearly due to liver damage. Hepatic necrosis is a frequent cause of death in paracetamol overdose. Addy's leading article in the *BMJ*[16] concluded that when an antipyretic drug is required in children, paracetamol is to be preferred to salicylate. A recommendation to avoid a drug that has been used for 80 years is perhaps premature if the data on Reye's syndrome are the reason.

The treatment of Reye's syndrome is non-specific and has controversial elements. The aims are to minimise the metabolic abnormalities and prevent an increase in intracranial pressure.[2] Assessment of the relative importance of different aspects of treatment regimens is difficult, since the disease runs a continuum of severity from relatively mild cases which never progress beyond mild drowsiness to patients who rapidly become decerebrate and die within a few hours of onset.[2 5] The outcome is also related to the severity of disease at the time of admission.[2 4 5 32] Nevertheless, units with a lot of experience in the management of this disorder have developed protocols which allow them to obtain negligible mortality and low morbidity.[2] Patients in whom the neurological symptoms have not progressed beyond the stage of lethargy with slow thought processes usually require only correction of any fluid and electrolyte deficit and the maintenance of a blood sugar concentration above 8 mmol/l (144 mg/100 ml) with infusions of 10-15% glucose. The total fluid intake should be limited to about 70% of the normal daily requirement. Patients unresponsive to verbal stimuli or light pain require intensive medical and nursing management. Fluids and glucose should be given at rates which control the blood sugar at 8-10 mmol/l and the serum osmolality at 300-320 mmol (mosmol)/kg. The intracranial pressure, measured subdurally or by an intraventricular catheter, should be lowered to maintain a cerebral perfusion pressure of at least 50 mm Hg. The key measures in controlling intracranial pressure are assisted ventilation with paralysis, maintaining the arterial carbon dioxide pressure at 3·3 kPa (25 mm Hg), phenobarbitone and morphine coma, and nursing the head raised at 40°. The places of dexamethasone and mannitol are controversial. Bifrontal decompressive craniotomies may be considered if these measures fail.

The best results of treatment have come from centres in which there is an increased awareness of Reye's syndrome, both in the community and on the part of doctors, resulting in the diagnosis of milder cases and earlier introduction of treatment. A national survey of Reye's syndrome being conducted in Britain,[7] and the emergence of parent based organisations interested in Reye's syndrome can only help in this regard. One parent based organisation is: the Michael McGough Foundation Against Liver Disease in Children (charity No 280814), PO Box 494, Western Avenue, London W3 0SH.

A P MOWAT

Consultant Paediatrician,
King's College Hospital Medical School,
London SE5 8RX

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Treating the menopause

The guidelines for community menopausal clinics presented by the Family Planning Association (p 2033) show another facet of the association's activities that has been developed since the National Health Service took over its family planning clinics. These are sensible administrative recommendations, but the long term aims of the treatment are still not clear. The crucial question is whether treatment should be confined to symptoms related to the perimenopause just as long as they last or whether it should attempt the long term prophylaxis against osteoporosis.

Medication may be difficult to maintain because of poor long term compliance if prophylaxis is the main objective. The regular withdrawal bleeds induced by the oestrogen-progestogen combination may upset patients and general practitioners, and gynaecologists may be unwilling to provide their supervision. A further disincentive for the patient is the need to have an endometrial aspiration before treatment and at intervals later. A long term prophylactic regimen might be more acceptable if it were possible to predict those who may ultimately develop osteoporosis, as each patient would then have much more to gain. Clinical judgment may suggest the asthenic, fair, coffee drinker as the most likely victim, but no laboratory test is readily available—though screening with labelled diphosphonate has been suggested as a predictive test of spinal osteoporosis.[1]

Our present approach attempts to treat all perimenopausal women, recognising that only half those aged 50-55 have symptoms[2] (indeed, only half have symptoms even after oophorectomy)[3] and in only 10% are they severe enough to interfere with life style.[4] No correlation has been attempted between symptoms and the ultimate development of osteoporosis, though symptoms are associated with lower circulating concentrations of oestrone and oestradiol than are found in asymptomatic women.[5]

Yet osteoporosis is clinically very important: its long term ravages are striking. One quarter of all women over the age of 60 will develop spinal compression and one fifth will suffer a fractured hip by the age of 90. Put another way, four out of five elderly women with hip fractures have osteoporosis and one in seven will die within three months.[6] The data of Lindsay *et al* on women who had had a hysterectomy and bilateral oophorectomy and were being treated with ethinyloestradiol alone showed that if treatment was begun within two years of this precisely defined artificial menopause (the naturally occurring state is more difficult to define) the loss of bone was arrested and that by eight years later the treated and non-treated groups differed substantially.[7] If the treatment was stopped, however, there was a rapid loss of bone to the level of the untreated women at the same stage after the menopause. This is an important finding—implying that there is little long term benefit unless the treatment is maintained for a time sufficient to delay osteoporosis. The patients of Lindsay and colleagues did not have their uteruses and so had no worries about endometrial carcinoma, and they did not have the aesthetic problems of the long term maintenance of regular withdrawal bleeding. Indeed, implants of oestrogen would have been an effective alternative treatment.[8] They were also younger than the mean age of menopause in Britain (50·8).[9]

If, then, as seems possible, 10 to 15 years' treatment is required to defer the impact of osteoporosis women will need to be encouraged to take treatment until perhaps the age of 65. Treatment has proved acceptable in the short term in highly motivated younger women supported by convinced doctors, but there is little evidence for its long term acceptability in the older woman who still has her uterus. Anxiety about endometrial carcinoma has been reduced recently with the addition to the oestrogen of a sequential progestogen, which appears to prevent adverse endometrial change if given for 10 days.[10] All carcinomas found by Thom *et al* in 850 patients were in the pretreatment biopsy specimens,[11] and with the acquisition of more data it may be possible ultimately to dispense with follow up biopsies.

Is there an alternative? The case for non-hormonal treatment of osteoporosis has recently been made in the *BMJ*.[12] Possibly a predisposing cause of osteoporosis may be a suboptimal dietary intake of calcium exacerbated by a high fibre diet. If this is true calcium supplements might become routine in prophylaxis, with treatment with a microcrystalline hydroxyapatite compound reserved for patients with established osteoporosis. Regimens using sex hormones and calcium and 1α-hydroxyvitamin D_3 are comparable in maintaining calcium balance in patients with spinal osteoporosis.[13] In the light of medical and consumer doubts about the widespread use of prophylactic sex steroids to prevent osteoporosis what is needed is a prospective controlled trial of sequential oestrogen-progestogen versus calcium and 1α-hydroxyvitamin D_3 in women with a spontaneous menopause. An assessment of long term acceptability would be important for both the bleeding component and the "mental tonic" effect[14] induced by the steroids. These aspects may prove critical in determining the response of women at large.

While these symptomatic effects may determine acceptability the objective of treatment would remain the prevention of osteoporosis and ultimately fractures. If the regimen using calcium and 1α-hydroxyvitamin D_3 were effective then shorter term treatment with sex hormones might be selected as the optimum control of symptoms with non-sex hormone treatment used as long term prophylaxis. Each may then be seen to be complementary, and the regimens could be implemented in community menopausal clinics.

I D COOKE

Professor of Obstetrics and Gynaecology,
University of Sheffield,
Jessop Hospital for Women,
Sheffield S3 7RE

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