REVIEW ARTICLE

Reye's syndrome: a clinical review

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Reye's syndrome is a virus-associated biphasic disease that causes acute encephalopathy in infants and children. Epidemiologic and experimental data support the hypothesis that it is a multifactorial disease of modern civilization. Just as young patients seem to be recovering uneventfully from the first phase of the illness, usually a nonspecific viral-like illness such as a respiratory tract infection or gastroenteritis, the second phase, encephalopathy, starts unexpectedly, with vomiting and sensorial changes. Identifying the syndrome early in the second phase and referring the child to a specialized centre with the experience, staff and facilities to manage this phase has improved the numbers and neurologic condition of survivors, though the overall mortality is still about 20%. Therapy is primarily directed at facilitating adequate cerebral perfusion pressure.

Le syndrome de Reye est une maladie diphasique de nature virale qui cause une encéphalopathie aiguë chez les nourissons et chez l'enfant. Les données épidémiologiques et les résultats expérimentaux soutiennent l'hypothèse d'une affection multifactorielle de la civilisation moderne. Juste comme les jeunes malades semblent se remettre sans incident de la première phase de la maladie, habituellement une affection non spécifique ressemblant à une maladie virale telle qu'une infection respiratoire ou une gastro-entérite, la seconde phase, une encéphalopathie, débute sans avertissement par des vomissements et des troubles de la conscience. L'identification précoce du syndrome dans sa deuxième phase et le transfert de l'enfant dans un centre spécialisé possédant l'expérience, le personnel et les moyens nécessaires pour s'occuper de cette phase a permis d'améliorer le nombre et l'état neurologique des survivants; toutefois la mortalité globale est encore d'environ 20%. Le traitement consiste d'abord à faciliter une pression de perfusion cérébrale adéquate.

Although cases of encephalopathy and fatty degeneration of the liver and other viscera have been reported sporadically since 1929,[1-3] it was not until 1963 that an Australian pathologist, Douglas Reye, clearly defined the clinical and pathological features of this unique childhood syndrome.[4] Retrospective surveys of autopsy records suggest this disease entity was reported only infrequently prior to the 1950s.[5] However, the number of case reports increased steadily through the late 60s and early 70s, and Reye's syndrome could no longer be considered a rare disease. By 1974 the frequency of reported cases was second only to that for acute infectious encephalitis among virus-associated causes of death from central nervous system disease in childhood.[6]

Reye's syndrome occurs almost exclusively in children. The clinical course is biphasic: initially the child appears to be recovering uneventfully from a viral illness, such as varicella or influenza; the sudden onset of vomiting heralds the beginning of the second phase. Symptoms and signs of central nervous system dysfunction characterize the progression of the syndrome. Fluctuating personality changes and deterioration in the level of consciousness are early symptoms, and it is usually at this stage that the child is brought for medical attention. As the encephalopathy becomes more acute, extreme irritability, agitation and even combative behaviour may alternate with lucid intervals of appropriate behaviour. The child's level of awareness may also fluctuate, but can rapidly slip from mild confusion to delirium and coma. Convulsions may occur early, particularly in infants. The rapidity and the extent of deterioration in central nervous system function varies from patient to patient: the severely affected child can be comatose and have decerebrate posturing within hours of the onset of vomiting.

Although the ratio of fatalities to cases has been falling,[7] the mortality is still in the range of 20%.[8] While some of the decrease in mortality is probably due to increased reporting of nonfatal cases and the recognition of earlier and milder cases of the syndrome, there is evidence that earlier treatment and improvements in therapy have also contributed to this decrease.[7,9,10]

The photographs on the cover of this issue of the Journal, supplied by Dr. Crocker and the Izaak Walton Killam Hospital, depict a young patient with Reye's syndrome who has an intracranial monitor in place, and the typical fatty liver from a case of this syndrome.

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Incidence and epidemiology

The incidence of Reye's syndrome is related to the prevalence of influenza B in the community and is approximately doubled during influenza B epidemics.[7,11] Corey and colleagues[12] estimated the incidence of Reye's syndrome in schoolchildren under the age of 18 to be 0.3 to 0.6/1000 cases of influenza B, or approximately one case of Reye's syndrome for every 2000 children with influenza B during epidemics. For some reason the incidence of Reye's syndrome in the population at risk is four times greater in rural areas than in urban areas, a finding that cannot be accounted for by the geographic distribution of influenza B infections during epidemics.[12]

Epidemiologic data for Canada are unavailable. In the Maritimes, where the incidence varies from province to province, we have estimated the rate per 100 000 population under the age of 18 years to be 0.75 in New Brunswick and 0.09 in Nova Scotia on the basis of histologically confirmed cases seen over the 7-year period 1970–1976.[13] Unfortunately, age-specific attack rates for influenza B are not available for these years, so comparison with data from the United States is not possible. Voluntary reporting from 39 states during 1977–1978, when influenza B was not prevalent, revealed an incidence of Reye's syndrome of 0.37/100 000 population in each age group at risk.[7]

Reye's syndrome is a disease of infancy, childhood and adolescence, and there is no sex predilection. From Dec. 1, 1977 to Nov. 30, 1978 in the United States the mean age for all children with Reye's syndrome was 8 years, and the range 4 months to 17 years.[7] Of these children 56% initially had respiratory symptoms and 29% varicella; in these two groups most were 5 to 9 years old. The cases of Reye's syndrome associated with outbreaks of influenza B have tended to occur more in children older than 9.[1] These differences could reflect the age-specific attack rates of these antecedent viral illnesses.[7]

Three types of antecedent illnesses have generally been reported: upper respiratory tract illness, chickenpox and gastroenteritis. In addition to the influenza B and varicella viruses, other viruses have been implicated including reoviruses 1 and 2, echoviruses 2, 8 and 11, coxsackieviruses A, B_4 and B_5, adenoviruses, the herpes simplex virus, influenza A_2 virus, parainfluenza virus, cytomegalovirus, rhinoviruses and the Epstein–Barr virus.[14] It has been suggested that live virus vaccines may occasionally serve as cofactors in the pathogenesis of Reye's syndrome, but conclusive epidemiologic evidence has not been reported.[15,16]

The geographic distribution of influenza B virus among the population at risk does not explain the predominantly rural distribution of Reye's syndrome,[12] nor can the distribution of the viral infection explain the racial differences in the attack rates for Reye's syndrome:[7] 86% to 90% of all cases of Reye's syndrome occur in white children over the age of 1 year, regardless of the viral or viral-like prodrome.[7,17] For unknown reasons Reye's syndrome occurs more frequently in black than in white infants every year. During 1977–78, for example, when influenza B illness was not prevalent, 64% of all infants with Reye's syndrome were black and 53% of black children of all ages with Reye's syndrome were infants.[7] The higher incidence of Reye's syndrome in black infants does not appear to be associated with any specific viral agent.[7] In Quebec the proportion of infants among all children with Reye's syndrome is also high: 10 of 22 affected children seen at Ste. Justine Hospital in Montreal were less than 1 year old.[18]

Pathogenesis

Four concepts of the pathogenesis of Reye's syndrome currently have prominence. The illness is considered to result from:

- An intrinsic toxin that affects mitochondrial metabolism and, secondarily, other cellular metabolic functions.
- An extrinsic toxin that alters the host's response during recovery from a viral illness.
- A genetic susceptibility to Reye's syndrome following exposure to a specific viral or viral-like disease.
- A primary defect in lipid and ammonia metabolism that results in cerebral edema and coma following viral or viral-like exposure.

Though these concepts are often discussed singly, it is probable that all contain an element of validity. For example, genetic susceptibility can be considered a predisposition, viral infection a triggering factor, and altered lipid and ammonia metabolism a mediator. Certainly viral exposure has been common to all cases and appears to be essential for development of the syndrome.

Why most children who manifest this unique response on one occasion fail to have similar episodes following subsequent viral illnesses is unexplained, but it seems likely that extrinsic toxins act as primary factors. Current research has increased our understanding of the effects of such virus–chemical interactions on cell metabolism,[19,20] but further research into the changes that occur at the molecular level within the cell are needed before we can differentiate the cellular changes that are nonspecific from those that are causal.

Ultrastructural analysis of the cells and cell biology studies have demonstrated transient disturbances in mitochondrial function in Reye's syndrome.[8,21-23] Aprille[21] has demonstrated a substance of low molecular weight in the serum of patients with Reye's syndrome that acts to alter mitochondrial metabolism. Although this factor was first thought to be unique to Reye's syndrome, it has subsequently been found in other conditions, such as Chédiak–Higashi syndrome, chickenpox and hepatic coma.[24] Recently the main component of this intrinsic factor was identified as uric acid.[25] Probably the sick child is simply retaining the byproducts of cell metabolism, but this is one way in which mitochondrial dysfunction can occur in Reye's syndrome.

The predominantly rural distribution of Reye's syndrome, the clustering of cases in certain regions, and the inexplicability of this clustering on the basis of the incidence

of viral diseases in the population have led investigators to question whether extrinsic environmental factors can alter the child's response to viral infections. Friend and Trainer,[26] Colon and associates,[27] Bourgeois and coworkers,[28] and Crocker and colleagues[19,20] have shown that various extrinsic factors, such as polychlorinated biphenyls, aflatoxin, 4-pentenoic acid and pesticide emulsifying agents, are capable of causing a lethal fatty visceromegaly in animals. However, the relevance of these observations to Reye's syndrome has been difficult to establish, as many of the steps in the biologic sequence that occurs in the child with Reye's syndrome have not been satisfactorily demonstrated in the animal models. Nevertheless, the basic biologic fact of a viral–toxic synergistic interaction has been established in both animal models and human tissue cultures.[20]

It has been suggested that genetic factors affect a child's susceptibility to Reye's syndrome following viral infections, as the syndrome has been reported in twins,[30] siblings[31] and the offspring of first-cousin marriages.[32] Abnormal pancreatic function has been noted in Reye's syndrome survivors and in their relatives,[33] and it has been theorized that this abnormality may identify families with an inherited factor that predisposes them to Reye's syndrome. However, such a genetic predisposition would not explain the rural clustering of Reye's syndrome, and one would expect a much higher rate of recurrence of the syndrome than has been reported.

Though there have been many enzyme deficiencies reported in Reye's syndrome, these have only been apparent during the acute phase of the disease. Thaler and colleagues[34] originally described a patient with Reye's syndrome whose ornithine transcarbamylase level was depressed during the acute illness and remained depressed following complete recovery from the syndrome, but Snodgrass and DeLong[35] were unable to correlate the changes in these levels with the clinical course of Reye's syndrome; as well, Brown and coworkers[22] have demonstrated that the changes in levels of ornithine transcarbamylase seen in children with Reye's syndrome are transient. While there is no question that the urea cycle enzymes are depressed during the acute phase of the illness, the child originally described by Thaler and associates[34] probably had an inherited deficiency of ornithine transcarbamylase and presented with a syndrome similar to Reye's.

Factors responsible for brain edema and coma induction may be related to defects in lipid and catecholamine metabolism. Markedly elevated concentrations of homovanillic acid in the ventricular fluid of patients with Reye's syndrome have been demonstrated by Shaywitz and associates[36] and suggest a defect in the monoaminergic system. In a previous study Lloyd and colleagues[37] found that the octopamine levels in the brain tissue of Reye's syndrome patients were increased, indicating a defect in neurotransmitter substances. Alterations in both amino acid and lipid metabolism have been consistently reported in Reye's syndrome patients. However, although the short-chain fatty acids can induce coma when infused into young rabbits,[38] ammonia must be combined with the fatty acids to have the same effect in dogs,[39] and in humans the mechanism of coma induction is still not clearly understood.

Clinical presentation

Reye's syndrome is a medical emergency. Unfortunately, there are few specific findings to help the physician differentiate the syndrome from acute encephalopathy of other causes. Nevertheless, when the clinical course of the disease is biphasic, with an antecedent viral-like illness and with vomiting at the onset of the encephalopathy, this diagnosis should be considered. Dilated pupils and hyperventilation are frequent in children who have become semicomatose, and the liver enlarges slightly early in the illness in 30% of cases. Children with Reye's syndrome are not jaundiced, and most will not have any signs or symptoms that reveal their hepatic dysfunction. Therefore, it is extremely important that serum transaminase concentrations be determined in all children with acute encephalopathy of unknown origin.

The clinical presentation of Reye's syndrome differs with age. The most common prodrome in infants is gastroenteritis, whereas in older children upper respiratory tract infections and varicella are the most common antecedents. In infants tachypnea, respiratory distress and seizures are more common early in the clinical course, and vomiting is rarely as prominent or protracted as it is in older children.[40] Hypoglycemia is also more common in infants; the eight infants reported by Huttenlocher and Trauner[40] all had hypoglycemia, and in 79% of the 59 cases in infants they reviewed the blood glucose level was less than 2.8 mmol/l (50 mg/dl). The mortality and the risk that survivors will have severe neurologic impairment are increased in infants.[18,40] As cerebral edema is a lesser problem in the infant, this poorer prognosis suggests that infants are more susceptible to brain cell damage from the acute metabolic disturbances of the syndrome.

Regardless of the patient's age, it is possible to separate most cases of Reye's syndrome from cases of acute encephalopathy of other causes by demonstrating hepatic dysfunction.[5,41] When children with the syndrome are first seen the serum transaminase levels are raised. As well, in 90% the blood ammonia level is raised and the prothrombin time is prolonged.[9,18,40-45] The serum transaminase levels rise early in the course of the disease, usually preceding the rise in blood ammonia levels.[46] The ammonia levels increase to a peak during the first 2 to 3 days following the onset of vomiting,[46] but then decline quickly and may reach normal levels within 24 to 72 hours after the child is admitted to hospital.[45-49] Normal blood ammonia levels have occasionally been reported in patients with mild disease,[42,45] though it is conceivable that a blood sample obtained either too early or too late in the course of the illness could have a normal ammonia level. Nevertheless, persistently normal blood ammonia levels are unusual, and patients who do not show raised levels need a liver biopsy before Reye's syndrome can be diagnosed.

Strictly speaking, the diagnosis of Reye's syndrome cannot be established unequivocally without a liver biopsy. However, as this is not always practicable, it has been necessary to develop guidelines for an accurate, early diagnosis to facilitate patient care and to improve the collection of epidemiologic data. The conditions considered necessary for establishing a diagnosis in the absence of histologic confirmation are:[42]

- A clinical history of a biphasic illness with a preceding viral-like prodrome.
- A noninflammatory nature to the acute encephalopathy (fewer than 10 cells/mm^3 of cerebrospinal fluid).
- Biochemical evidence of hepatocellular dysfunction: at least a 200% increase in the serum transaminase levels and a 150% increase in the blood ammonia level.
- The exclusion of other causes of acute encephalopathy and hepatocellular dysfunction (Table I).

Laboratory investigations

If the diagnosis of Reye's syndrome has been made without confirmation by means of a liver biopsy, cerebrospinal fluid should be obtained with a small-bore needle for tests to exclude a treatable infectious disease. For example, bacterial meningitis can present as an acute nonspecific encephalopathy, and it requires both prompt diagnosis and specific therapy. A lumbar puncture to obtain cerebrospinal fluid may be one of the earliest diagnostic procedures performed on a child with such a condition and is often done before serum transaminase or blood ammonia levels can be determined. Because cerebral herniation is always a threat in patients with increased intracranial pressure, we frequently infuse mannitol intravenously before doing a lumbar puncture. In the later stages of Reye's syndrome we may request neurosurgical assistance to drain off fluid with a direct tap.

As other diseases can produce encephalopathy, a rise in serum transaminase levels and other signs of hepatocellular dysfunction (Table I), a liver biopsy is essential to establish a definitive diagnosis. Frozen sections of the liver tissue, stained to identify fat cells, will demonstrate a panlobular distribution of microvesicular fat in every liver cell, and formalin-fixed sections will show that the hepatocyte nuclei are not displaced by this fat. There will be very little inflammatory change or individual liver cell necrosis. Though centrilobular necrosis has been reported, it is unusual, and Bove and associates[5] considered it to be a superimposed change rather than a feature of the syndrome itself. Electron microscopy may demonstrate typical changes and is important for the retrospective analysis of cases,[23,41] as Reye's syndrome without fatty liver has been described,[64] and the distribution of small fat droplets in liver cells has been reported in syndromes resembling Reye's.[43,61,62] When possible a liver biopsy should be obtained within 3 to 4 days after the onset of the encephalopathy, as the histologic features may not be as characteristic later.[41] Vitamin K_1, fresh frozen plasma or exchange transfusions may be required to correct the prolonged prothrombin time before a percutaneous liver biopsy is performed.

The prolonged prothrombin time in patients with Reye's syndrome is often associated with hypofibrinogenemia and decreased levels of liver-dependent coagulation factors.[16,65] However, the platelet count is usually normal, and evidence of clinical bleeding is unusual,[41,63] as is transient disseminated intravascular coagulation.[64] Though the hemoglobin levels and erythrocyte shape and number are usually normal,[55] the leukocyte count can range between normal and 20 to 40 $\times$ 10^9/l,[66-68] yet cultures of blood and cerebrospinal fluid have given negative results.[10,66]

When the encephalopathy has advanced to the stage where the patient is delirious or behaving combatively, hyperventilation commonly occurs. This may result from either respiratory alkalosis or mixed respiratory alkalosis and mild metabolic acidosis, so blood-gas values should be determined early. Severe metabolic acidosis is unusual at the onset of the syndrome[41,55] but is not uncommon in the terminal phase. The blood urea nitrogen and serum creatinine levels are usually normal or only mildly raised,[66,68] but renal failure has been reported.[67]

Some intoxications can present with a Reye's-like syndrome, including those caused by isopropyl alcohol,[69] aflatoxin[70] and valproic acid.[71] Screening of the patient's urine and blood will reveal these

Table I—Differential diagnosis of a Reye's-like syndrome

- **Infections**
  - **Meningitis**[42]
  - **Hepatitis**
  - **Viral encephalitis**[42]
  - **Septicemia due to *Yersinia pestis***[50]
  - **Salmonellosis**[51]
- **Intoxications**
  - **Jamaican vomiting sickness**[52]
  - **Salicylate intoxication**[53,54]
  - **Chlordane intoxication**[54]
  - **Disulfiram intoxication**[54]
  - **"Out-dated" tetracycline**[55]
  - **Phenformin intoxication**[55]
  - **Pyrrolizidine (Senecio) intoxication**[56]
  - **Methyl bromide intoxication**[57]
- **Metabolic diseases**
  - **Ornithine transcarbamylase deficiency**[58]
  - **Systemic carnitine deficiency**[51]
  - **Suspected defect in fatty acid oxidation**[59]
- **Acute illnesses with hepatocellular disease and encephalopathy**
  - **Hypoxic encephalopathy and anoxic liver damage**[40,55]
  - **Centrilobular necrosis with shock, or of unknown cause, associated with encephalopathy**[60]
  - **Viral infections associated with noninfectious illnesses or their sequelae**
    - **Encephalopathy associated with cold-agglutinin autoimmune hemolytic anemia**[61]
    - **Adenovirus type 7 pneumonia with extensive extrapulmonary disease**[62]
- **Other conditions in infants**
  - **Sudden infant death syndrome**[42]
  - **Respiratory distress**[40]
  - ***Shigella* enterocolitis and endotoxic shock**[63]

substances and may reveal salicylate, acetaminophen or antiemetic drugs[42] when they are responsible for the patient's condition.

Raised serum and urine amino acid levels[4,66] and the excretion of organic acids[66] are seen in Reye's syndrome, and hyperaminoacidemia is said to be characteristic;[44] however, we have not found the pattern to be specific enough to establish the diagnosis without a liver biopsy. As some metabolic diseases associated with hyperaminoacidemias can present with a Reye's-like syndrome, it is particularly important to exclude these conditions in infants by determining amino acid patterns.

The results of electroencephalography, though abnormal, are not usually specific for Reye's syndrome. Nevertheless, the abnormal features have been staged and are of prognostic value.[47] With the current emphasis on earlier and more aggressive intervention, electroencephalography can assist in staging the severity of the encephalopathic process. Electroencephalographic patterns have been grouped into normal; borderline abnormal; abnormal, grades 1 to 5; and, in the terminal stage of the disease, electrocerebral silence.[47] Deterioration of the electroencephalographic pattern often precedes deterioration in the clinical state. Aoki and Lombroso[47] initially reported that all children with grade 1 and 2 abnormalities survived, whereas a large proportion of children with grade 4 and 5 abnormalities either died or survived with a severe neurologic handicap. This correlation of electroencephalographic staging with prognosis has been confirmed by a number of investigators.[18,46]

Our clinical staging (Table II) of the encephalopathy in children with Reye's syndrome follows the modifications of Lovejoy and coworkers[46] to Plum and Possner's classification.[72] Similar systems are in use in most centres,[43] but the lack of uniformity between centres in the staging criteria has been criticized.[73] The staging, based on the cephalad–caudal progression of brain stem dysfunction that occurs with increasing depth of coma, allows us to evaluate various forms of therapy in children with different degrees of severity of clinical illness (Table II).

Children whose disease is in clinical stage IV or V, or is rapidly progressing from stage I to stage III, have a poor prognosis.[17] Unfortunately, the severity of the coma also correlates positively with the possibility of residual neurologic dysfunction. A 1973–74 study showed that of the survivors who had reached a stage IV or V coma during their illness 30% had a residual neurologic deficit.[17] Brunner and colleagues[74] observed an association between the severity of the encephalopathy and future behaviour patterns: they found that 85% of those who had had an initial coma stage of 3.2 or greater had problems in school. Electroencephalogram patterns also correlate with neurologic outcome: Vancaillie and Lovejoy and their associates[18,46] have reported significant neurologic sequelae following abnormalities of grade 3 or greater.[47]

Age appears to be a prognostic factor as well. In an early review Bradford and Latham[66] reported a 95% mortality in children under the age of 2 years. Davidson and associates[75] found the highest percentage of psychomotor abnormalities in children who had had Reye's syndrome during the first year of life, though there were few children older than 3 years in their series. A review of all the infants with Reye's syndrome in a 1978 report revealed that this age group had a mortality of 61%, and among those who survived the incidence of severe neurologic sequelae was 15%.[40]

An initial blood ammonia level of more than 176 μmol/l (300 mg/dl) has been associated with a significant increase in mortality.[17,49] An increase in the level of creatine phosphokinase in the serum, suggesting extensive involvement of

Table II—Clinical staging of encephalopathy in Reye's syndrome

Feature	Stage I	Stage II	Stage III	Stage IV	Stage V
Level of consciousness	Quiet and drowsy, responds to commands; vomiting	Combative behaviour alternating with mild delirium, not responsive to verbal communication, responds purposefully to pain	Early onset of coma, decorticate posturing, decorticate response to pain	Deepening coma, decerebrate rigidity, extensor response to pain	Deep coma, flaccidity, paralysis
Pupils	Normal	Dilated, but quickly responsive	Dilated, but quickly responsive	Dilated and slowly responsive; may be unequal	Fixed and dilated
Ventilation	Usually normal, but may have central hyperventilation	Hyperventilation	Hyperventilation	May lose spontaneous respiratory activity	No spontaneous respirations
Electroencephalographic grade[47]	Normal to 1	2 or 3	3 or 4	3 or 4	5 or electrocerebral silence
Reflexes:					
Oculocephalic	Normal	Normal	Normal	Lost	± spinal reflexes only
Ciliospinal	Normal	Normal	Lost	Lost	
Babinski	±	Extensor	Extensor	Extensor	
Doll's eye	Normal	Normal	Normal	Lost	
Ice water caloric	Response	Response	Response	Response	

both muscle and liver,[16,42] particular patterns of hyperaminoacidemia,[44] persistent hypoprothrombinemia,[8] severe metabolic acidosis[8,42] and worsening of the electroencephalographic pattern have all been correlated with a poor prognosis.

Both early diagnosis and early therapeutic intervention can contribute to a decrease in mortality.[7,10,17] Children who respond to verbal stimuli or light pain — that is, those who appear clinically to be in stage I or II — do well with supportive therapy only, and the survival rate for children in these stages is now approaching 100% in specialized centres.[41,43] The overall mortality in the United States between Dec. 1, 1977 and Nov. 30, 1978 was 15% for stage I cases and 42% for stage II cases.[7] This suggests a need for close observation and careful treatment of children with even a mild illness.

Treatment

Although Reye's syndrome is associated with a complex variety of metabolic disturbances,[8,65] both death and the neurologic sequelae in survivors are attributed to the insult to the central nervous system. Therefore, therapy is focused on maintaining an adequate cerebral perfusion pressure while providing the support required to minimize the associated metabolic dysfunction.

Patients in clinical stage I or II usually only require correction of fluid and electrolyte deficits, and maintenance intravenous therapy with a 10% glucose solution. All patients with Reye's syndrome should be monitored closely in an intensive care setting, as their clinical condition can deteriorate rapidly, even in mild cases.

Patients not responding to verbal stimuli or light pain are seriously ill and require more aggressive management: details of management vary somewhat in different centres,[9,10,41,55,76,77] but early diagnosis, constant monitoring and a well organized supportive care plan are important common features.[78] Data from centres that specialize in the care of Reye's syndrome patients have revealed superior survival rates.[10,79] The success of their approach appears to depend on early diagnosis and on prompt referral of affected children.

Children severely affected by Reye's syndrome require the following:

- Endotracheal intubation.
- A mechanical respirator to control hyperventilation and maintain the arterial carbon dioxide pressure at 25 to 30 mm Hg.
- Pancuronium bromide, 0.1 to 0.2 mg/kg, to combat muscle paralysis and thus facilitate adequate mechanical ventilation.
- A central venous or Swan–Ganz catheter. If the blood volume is depleted it should be expanded with the appropriate colloid solution. Any electrolyte imbalances should be corrected. If a Swan–Ganz catheter is used the pulmonary artery wedge pressure should be maintained at 3 to 5 mm Hg.
- Intravenous fluids with 15% to 20% glucose, delivered at a rate of approximately 1200 ml/m^2 of body surface area in 24 hours. The blood glucose level should be kept between 8.3 and 10.0 mmol/l (150 and 180 mg/dl).
- A ventricular, subdural or subarachnoid monitoring device to continuously record the intracranial pressure. If the patient has a prolonged prothrombin time, fresh frozen plasma or a partial exchange transfusion can be used to minimize the bleeding.
- An arterial line to monitor both arterial pressure and arterial oxygen concentration. To provide adequate cerebral perfusion pressure (mean arterial pressure minus intracranial pressure), at least 50 mm Hg, the mean arterial pressure should be greater than 90 mm Hg and the arterial oxygen pressure between 100 and 150 mm Hg.
- A cooling blanket, if necessary, to keep the body temperature at 37°C.
- When the intracranial pressure is greater than 20 mm Hg, mannitol, 0.25 g/kg as a 20% solution, given intravenously over 10 to 20 minutes. In acute situations, the most effective means of rapidly lowering the intracranial pressure while waiting for the mannitol to become effective is manual hyperventilation.
- Monitoring of the serum osmolality every 4 hours to keep it below 320 mOsm/kg.
- If the intracranial pressure cannot be reduced with mannitol, or if the serum osmolality is greater than 320 mOsm/kg, induce a coma with either phenobarbital[80] or pentobarbital.[81] With phenobarbital, give 50 mg/kg by slow intravenous drip initially while carefully monitoring the blood pressure; for the next 3 days give 25 mg/kg·d in three divided doses. This should keep the blood level at approximately 5 to 7 mg/dl. With pentobarbital, give 3 to 5 mg/kg intravenously initially, then give 1 to 2 mg/kg·h. Titrate the dose to maintain a blood level of 2.5 to 4.0 mg/dl.
- If barbiturate coma fails to reduce the intracranial pressure, cool the body to 31 to 33°C.
- If the intracranial pressure is still high, consider a bifrontal decompressive craniectomy.
- Careful chest physiotherapy and endotracheal suction given every 2 hours. The child should be on his or her back, with the head elevated 20 to 30°. If either procedure raises the intracranial pressure, use hyperventilation during the suctioning or give mannitol beforehand. Morphine sulfate, 0.1 mg/kg, has also been reported to be effective in controlling such intracranial pressure changes.[77]
- Antacids, administered while the intracranial pressure monitoring device is in place.
- Antibiotics, administered while the intracranial pressure monitoring device is in place.

Others have described modes of therapy such as the use of neomycin, administered by nasogastric tube or as an enema, to minimize further increases in the blood ammonia level, and the use of dexamethasone to help control the intracranial pressure. Recent emphasis on the management of brain edema in Reye's syndrome therapy has had its problems and its critics. Whether the monitoring of intracranial pressure is beneficial or damaging will only be clarified by a large controlled study. Subarachnoid hemorrhage, ventriculitis and bacterial meningitis have been reported with the use of subarachnoid and

intraventricular monitoring devices,[78] and porencephalic tracts have been reported following the intraventricular insertion of a monitor.[82] Nevertheless, the clinical signs of increased intracranial pressure appear relatively late, and the early reduction of high intracranial pressure should be facilitated by monitoring and should improve both the numbers and the neurologic condition of survivors.

Because intracranial pressure is only one of the factors affecting cerebral perfusion its continuous control alone will not keep the cerebral perfusion pressure at 50 mm Hg or above.[83] The avoidance of hypotension and hypoxia are important as well.

The use of barbiturate coma to decrease intracranial pressure is also associated with significant hazards. It is essential to have an arterial pressure line in place, as barbiturates can produce significant hypotension and thus reduce the cerebral perfusion pressure. During barbiturate therapy the clinician loses the ability to assess the patient neurologically. The diagnostic assistance of electroencephalography is also rendered ineffective and, as blood levels do not necessarily reflect either brain or cerebrospinal fluid barbiturate levels,[84] adequate control of this therapy is difficult.

The use of steroids to control cerebral edema in patients with Reye's syndrome is based on the results of research in animals[85] and on previously well documented reports of their effects in treating other causes of cerebral edema, such as brain tumour, trauma and brain abscess. However, their cytolytic effect on the brain and the need for control data in Reye's syndrome patients have led some centres to discontinue their use. Other antiedema agents, as previously mentioned, are available and are now felt to give better control of the patient's cerebral edema.

It is said that if surgical decompression by partial craniectomy is to be beneficial, it must be done early in the course of the illness. Unfortunately, there are too few reports of this form of therapy to allow any meaningful discussion of its place in the management of patients with severe Reye's syndrome, but in children whose condition was rapidly deteriorating and in whom other measures were having little effect, there has been success with this form of therapy.

Conclusion

Difficulties in clinical research into Reye's syndrome have really centred on case definition and the criteria required for diagnosis. While all researchers agree that Reye's syndrome exists, a definitive diagnosis requires an examination of the ultrastructure of the cell, which is not always practical. Any element of uncertainty about the diagnosis, particularly when so many acquired and inherited diseases can present with very similar syndromes, makes exacting clinical research difficult. In addition, the transient nature of the illness, despite its lethal potential, requires studies to be carried out on children during an acute illness and over a short period. Cell metabolism is altered in many organs of the body, but rarely to the extent of cell death, and the mechanisms responsible for the production of these intracellular alterations are the key to our understanding, better treatment and future prevention of Reye's syndrome.

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continued on page 425

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REYE'S SYNDROME

continued from page 382

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