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Henry Ford Hospital Clinicopathological Conference

Encephalopathy and renal failure in a three-month-old infant

Participants
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Protocol: Dr. Hugh Walker, Department of Pediatrics, Henry Ford Hospital

Case Presentation

A three-month-old black male infant was brought to the Emergency Room by his mother on June 18, 1980 in a friend's car because of respiratory arrest that immediately followed a convolution at home. The mother gave mouth-to-mouth resuscitation until they arrived at the hospital where the infant was noted to be apneic with a heart rate of 60-80/minute and a temperature of 40.6°C.

The baby had been well until June 16 when his mother returned from work in the evening and found him irritable, congested, and coughing. He was restless throughout the night and was taken to the emergency room by his mother on June 18, 1980 in a friend's car because of respiratory arrest that immediately followed a convolution at home. The mother gave mouth-to-mouth resuscitation until they arrived at the hospital where the infant was noted to be apneic with a heart rate of 60-80/minute and a temperature of 40.6°C.

The infant was given Kayexalate rectal enema, 0.5U insulin, and Valium was given (2.5 mg), and convulsive activity stopped for periods of up to two hours. On June 19 Dilantin was administered, and on June 20 the Dilantin level was 1.8 mg%, and convulsive activity stopped after 48 hours. On June 19 the calcium was 5.2, and calcium gluconate was given. Fluids were begun at 750 cc's in 24 hours but with low urine output, then reduced to 350 cc's a day as D-10 in .45 saline with urine replacement volume for volume. On June 18 the urine output was 23 cc's, on June 19 350 cc's, and on June 21 285 cc's. Thereafter the urine output dropped to 0 on the fifth day. On June 19 the PT was 23/12.5, the PTT 60/26-42, and the Factor VIII level 18%. The infant's head circumference was remeasured and was 38 cm, where it remained. On June 20 the SGOT was 2920; SGPT, 902; serum osmolality, 369; blood glucose 427; BUN, 43; sodium, 165; blood ammonia, 62; hemoglobin, 8.5; haptoglobin, 4. Off the ventilator, blood gases were pO2, 46; sO2, 56; pCO2, 64; pH, 6.99; and bicarbonate 15 in the oxyhood at 60% oxygen. On the ventilator blood gases were pO2, 55; sO2, 83; pCO2, 28; pH,
This three-month-old infant was well until two days before admission when his mother returned from work in the evening and found him irritable, congested, and coughing. Cough is not a prominent symptom in young infants unless they have a serious disorder such as whooping cough, cystic fibrosis, tracheoesophageal fistula, or pneumonia. A young infant who coughs should receive special attention. Whooping cough, in particular, is potentially fatal in young infants who have a serious disorder such as whooping cough, cystic fibrosis, tracheoesophageal fistula, or pneumonia. Such a child may not have a typical whoop but has repeated episodes of paroxysmal cough. Nevertheless, early diagnosis and appropriate management with parenteral feeding will save most young infants with whooping cough (1).

The infant in this case was restless throughout the night, was taken to his pediatrician on June 17, received an injection of penicillin and a prescription for penicillin and Actifed. Throughout the day he did not take his formula well, vomited once, and continued to be irritable and febrile with temperatures between 100-102°F.

The management of febrile infants under the age of three months is a neglected subject in pediatrics, and very little is mentioned in Nelson's Textbook of Pediatrics about it. Many pediatricians handle this situation quite inappropriately.

The age of the child with fever is one of the most helpful facts to single out the infant at risk. Under three months especially, infants with fever are at an increased risk for invasive, life-threatening but potentially treatable infections. Of the children in this age group with a temperature of 101°F or greater, 20% or more may have life-threatening bacterial infections (2). One prospective study has shown that a serious infection in a young febrile infant cannot be reliably diagnosed by history, physical examination, or the screening tests commonly used in the outpatient setting (3). Such children must therefore be thoroughly evaluated with cultures of cerebrospinal fluid, blood and urine, and a chest radiograph. It is perfectly reasonable to admit these children and treat them with intravenous antibiotics until culture results have been received, especially infants less than eight weeks old. At this age, pneumococcal, group B streptococcal, and E. coli infections are common.

This child continued to be congested, irritable, and febrile. He did not eat well and continued to vomit. On the morning of his admission his mother noted that he had deep respirations for about an hour followed by convulsive activity in the right leg and left arm, which lasted 20 to 30 minutes and was followed by respiratory arrest. She gave him mouth-to-mouth resuscitation and brought him to the Emergency Room.

It is interesting to speculate upon the etiology of these deep respirations. Respiratory distress and an increased respiratory effort to compensate for poor lung compliance or increased airway resistance might have been interpreted as deep respirations. However, the later determination of blood gases indicates that this is rather unlikely. It is quite likely that the infant was indeed hyperventilating either in response to metabolic acidosis or as a result of central neurogenic hyperventilation due to an encephalopathy that would lead to respiratory alkalosis. Unfortunately, at this stage we do not know what the blood gas status was, but from the subsequent course I would guess that the child was hyperventilating in response to metabolic acidosis. The convulsions in the right leg and left arm, which showed no localizing pattern, indicate diffuse cerebral
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cortical involvement. The soft fontanelle indicates absence of gross intracranial hypertension. There was no external evidence of injury in this child. This is an important observation, because in an unexplained, devastating situation like that presented today the spectre of child abuse is always lurking in the background. However, I would think child abuse is very unlikely in the absence of retinal hemorrhages or a tense fontanelle or any external evidence of trauma. Continuous tremors were noted in all extremities, and the deep tendon reflexes were absent.

So far, then, we have a three-month-old infant who has been sick for a few days, probably with an infectious process. Invasive, life-threatening bacterial infections must always be considered early in such infants. Since we have no evidence of sepsis or meningitis, presumably the infectious process was viral. The striking clinical and laboratory findings indicated severe tissue damage. The tremendous elevation in CPK showing skeletal muscle pattern, as well as elevations in LDH and SGOT, suggest skeletal muscle injury or rhabdomyolysis. The elevated BUN and creatinine indicate renal failure, which could be prerenal due either to dehydration or a low cardiac output secondary to cardiorespiratory arrest and hypoxia. However, the dehydration was not impressive, and the elevation of BUN to this extent occurred too soon to be attributable to cardiorespiratory arrest. The urinalysis supports my impression that there was parenchymal renal involvement in this child. A determination of urine urea nitrogen (UUN) and a ratio of UUN to BUN of less than 10 to 1 would have proven tubular damage at this stage.

Whether this child had renal vein thrombosis or not is difficult to speculate, although it is not surprising to find renal failure in patients with rhabdomyolysis and myoglobinuria. The color of this infant’s urine is not mentioned, and although there were many RBCs, I would still like to know whether there was myoglobin in the urine or not. Metabolic acidosis could have been due to cardiac arrest and hypoxia due to a low perfusion state. However, in such situations one usually encounters lactic acidosis that results in a large anion gap contributed by lactic acid. Since the anion gap in the child, at least initially, was only 14 mEq/L, lactic acidosis was not indicated. The metabolic acidosis was probably due to muscle injury or renal insufficiency and in fact might have been the cause of the deep respirations the child showed earlier in the morning. The elevated serum sodium and chloride probably indicate increased, insensible water losses from fever and hyperventilation. Hypoglycemia, in spite of 25% dextrose administration, is not too unusual in patients with cardiopulmonary arrest, but it may also indicate decreased hepatic output of glucose. The CSF protein was elevated with 248 RBCs/cmm. If there was no xanthochromia, I am going to ignore this finding at this time, especially in the absence of cellular response, except to point out that herpes encephalitis is often associated with elevated protein and the presence of red cells in CSF without a leukocyte response. Elevated platelets may be a response to viral infection, but it is difficult to comment on the reason for prolonged clotting studies in the presence of normal Factor VIII and elevated platelets. This may be a result of hepatic dysfunction; however, Factor VIII and platelets can be normal early in disseminated intravascular coagulation (DIC), which cannot be ruled out at this time. The elevated fibrin degradation products are consistent with DIC or fibrinogen consumption from any cause.

The infant was treated with Kay exalate enema, 0.5 units of insulin, and potassium fell steadily to 4.5 mEq/L. A total of 48 mEq of sodium bicarbonate was given in the first 48 hours because of persistent severe metabolic acidosis. Again at this time, I would like to know what the anion gap was. There were multiple bleeding sites, and he continued to show evidence of severe diffuse encephalopathy leading to multifocal myoclonic seizures which subsided after very aggressive treatment with phenobarbital, Dilantin, and Valium. Hypocalcemia seen on the second day, with serum calcium of 5.2 mg/dl, again supports our initial impression of rhabdomyolysis. Low serum calcium was probably due to the deposition of calcium in the muscles. Renal failure continued, first oliguric, then nonoliguric, and finally anuric. Prolonged PT, PTT, and low Factor VIII levels later in the course were most likely due to DIC. A platelet count at this time would probably have been low if it was done.

After this everything just about crashed. There was irreversible and profound cerebral damage. The liver had enlarged from 2 cm on the first day to 5 cm on the second day and finally to 7.5 cm. SGOT increased remarkably with normal or minimally elevated blood ammonia. Ultimately, the child died with irreversible brain injury, renal failure, and acidosis. In short, the infant was ill from two days before admission, presumably with an infectious process; in the absence of specific blood cultures for bacteria, this infectious process was most likely viral. The clinical presentation and laboratory findings indicate a combination of various states, namely: rhabdomyolysis, diffuse encephalopathy, renal failure, hepatopathy, metabolic acidosis, DIC, and probably also myocardial insufficiency.

Rhabdomyolysis was first described by Meyer-Betz in 1910. The syndrome is still regarded as rather rare, but recently it has gained renewed attention. Many cases probably go unrecognized, especially when muscle symptoms are slight or totally absent, so that some patients may actually present with acute tubular necrosis of undetermined origin (4). In addition, the color of the dilute myoglobin solution...
does not differ very much from that of concentrated urine. Some cases of myoglobinuria may be ignored.

There are many known causes of rhabdomyolysis:

1) Inborn errors of muscle metabolism: Phosphorylase deficiency, phosphofructokinase deficiency, carnitine palmitoyltransferase deficiency
2) Viral infections: Influenza A and B, coxsackie, hepatitis B
3) Electrolyte abnormalities: Hyperosmolar states, hypokalemia
4) Trauma: Crush injuries
5) Toxins: Heroin, alcohol, industrial poisons
6) Malignant hyperthermia, cold injury
7) Autoimmune.

However, still quite a few cases are classified as idiopathic. In a young infant, we should consider inborn errors of metabolism involving muscle enzymes, such as muscle phosphorylase deficiency or McArdle's syndrome, muscle phosphofructokinase, and carnitine palmitoyltransferase deficiency. The diagnosis in this group of patients can be established only with appropriate muscle enzyme studies with muscle biopsies. In McArdle's syndrome, the muscle glycogen is increased. Other causes of rhabdomyolysis applicable to our patient are infections, especially with Influenza A and B and coxsackie viruses. Severe hypernatremia with sodium over 190 mEq/L and hyperosmolar nonketotic diabetic coma are also reported to cause rhabdomyolysis; however, the serum sodium in our patient was not high enough to be a causative factor. In addition, both cold injury and heat exhaustion can cause rhabdomyolysis.

Clinically, the patient may present with multisystem involvement. Skeletal muscles may be swollen and tender with flaccid paralysis. This child's generalized hypotonia and absent deep tendon reflexes may or may not have been related to rhabdomyolysis; they may simply have been a manifestation of severe central nervous system depression.

Although renal failure occurs quite commonly in children with rhabdomyolysis, the exact mechanism is not very well understood. In the animal models of glycerol-induced myoglobinuria in rats, the renal tubules appear to be plugged by myoglobin casts. However, the pressures observed proximal to these casts are low in contrast to the high pressures expected, if mechanical obstruction to the flow were the primary mechanism of renal failure. The most consistent findings in this animal model are reduced renal blood flow and total and single nephron filtration pressure. The pressure in efferent arterioles is low with elevated circulating renin. It is therefore postulated that myoglobin exerts a direct toxic effect on the juxtaglomerular apparatus causing renin release, elevated angiotensin levels, constriction in the afferent glomerular arterioles, and therefore a decreased glomerular filtration rate (5).

Sudden unexpected deaths have occurred in a number of children during episodes of rhabdomyolysis. Arrhythmias related to hyperkalemia with or without potentiation by low serum calcium may occur. Tuller reported that in a series of 17 patients with rhabdomyolysis all had clinical myocardial involvement (6). The incidence of cardiopulmonary arrest can be high, with autopsies showing rhabdomyolysis of the myocardium. If respiratory muscle involvement is present, respiratory insufficiency may require ventilatory assistance. Central nervous system dysfunction can range from agitation to convulsion to coma. The exact mechanism for central nervous system changes in rhabdomyolysis is not very well known, and these changes could just be a manifestation of a primary toxic agent.

The diagnosis of rhabdomyolysis depends upon demonstrating myoglobin in the urine and having laboratory evidence of elevated muscle enzymes and intramuscular contents. Spectrophotometry and ammonium sulfate solubility tests can identify myoglobin, but immunoelectrophoresis is the most reliable and accurate method of identification. Red blood cells may be present in small to moderate numbers in the urine. In addition to the red-gold pigmented casts, occasionally one may observe myoglobin crystals.

Laboratory determination reveals hypercalcemia, hyperphosphatemia, and hypermagnesemia, as the muscle breaks down and intramuscular contents are released into the circulation. After these changes take place, hypocalcemia may occur as calcium is deposited in the muscle. CPK, SGOT, and aldolase are remarkably elevated. Both creatine and creatinine are elevated. Creatinine is elevated out of proportion to the elevation in blood urea nitrogen. In adults, at least, this is reflected in the ratio of BUN to creatinine of less that 8 to 1, as creatinine is elevated much more than BUN. In children, however, since the serum creatinine is normally low, the ratio of BUN to creatinine will be proportionately higher.

As far as renal failure in this child is concerned, prerenal causes, namely dehydration, low cardiac output, and decreased GFR might have been contributory factors. However, I do not think these were the primary mechanisms. Similarly, we do not have any evidence that postrenal causes produced obstructive uropathy, although in a young infant this should always be considered. The clinical picture and urinalysis indicate parenchymal renal involvement, which may be due to myoglobinuria caused by rhabdomyolysis. However, with the available information...
we really cannot rule out renal vein thrombosis or microangiopathic glomerular involvement from DIC. Renal failure following a viral infection and hemolytic anemia in a child should also raise the possibility of hemolytic uremic syndrome (HUS), although this child’s hemolysis is not as impressive as one often encounters in HUS.

The encephalopathy exhibited is diffuse, with no localizing pattern. Although there is no cellular response in the CSF, viral encephalitis such as with herpes is still possible, especially in association with diffuse systemic changes and DIC. However, I would think this is unlikely. Causes of encephalopathy associated with metabolic acidosis in children should always include poisoning, especially with salicylates, and inborn errors of metabolism such as organic acidemias. This child had no history of excessive aspirin administration, although a ferric chloride test on the urine should always be performed in such a situation regardless of the child’s history or age.

One has always to consider the possibility of Reye’s syndrome in the differential diagnosis of an acute onset of encephalopathy with liver involvement. Typically, the child seems to be recovering from a trivial viral infection such as upper respiratory infection, gastroenteritis, influenza-like illness, or chicken pox. These are four common prodromal clinical illnesses. During this recovery phase, the child suddenly begins to vomit followed by alteration in sensorium that ultimately progresses to various grades of encephalopathy. Increased intracranial pressure and cerebral edema, which are characteristic of Reye’s syndrome, are not always present, but in most cases they determine the survival and neurological outcome. The laboratory evidence of Reye’s syndrome includes elevation of liver enzymes, most notably SGOT. Blood ammonia is often not always elevated, and PT and PTT are usually prolonged. Liver histology shows characteristic but by no means pathognomonic diffuse microvesicular fatty infiltration. Most patients with Reye’s syndrome are five to 15 years old, although infants can be affected.

Reye’s syndrome follows a different clinical and laboratory pattern in infants than in older children (7). In infants, the commonly observed features are convulsions, metabolic acidosis, shock, disseminated intravascular coagulation (DIC), hypoglycemia, and renal failure. Generalized seizures are uncommon in older patients but are quite common in infants. In older children, respiratory alkalosis is a manifestation of central neurogenic hyperventilation, while in infants metabolic acidosis and shock are more common. Hypoglycemia, which Reye originally observed frequently in his patients, is common in infants but not in older children. The clotting dysfunction in older children is mainly restricted to the prolongation of PT and PTT, while infants manifest DIC. Renal failure may occur in older children, usually later in the course, probably as a complication of treatment, whereas infants may manifest renal failure at the time of presentation.

Although the child presented today could perhaps qualify for the diagnosis of Reye’s syndrome, I think the term is applied very loosely in infants. Before making the diagnosis of Reye’s syndrome in a young infant, one must always carefully rule out any inborn errors of metabolism, viral or bacterial encephalopathy, and poisoning. Elevations in SGOT can be nonspecific and could occur in many clinical situations with liver and muscle involvement. Histopathology of the liver showing diffuse microvesicular fatty infiltration is highly characteristic of Reye’s syndrome, but similar changes may be observed in other clinical situations as well.

In summary, this child’s clinical course and laboratory findings are most consistent with an infectious process, most likely viral, causing rhabdomyolysis and its complications. Cardiorespiratory arrest might have been due to ventricular arrhythmia secondary to hyperkalemia, or possibly to myocarditis or myocardial rhabdomyolysis. Reye’s syndrome as the diagnosis of this child’s case may be offered only after a process of exclusion. Unfortunately, in similar clinical instances, the diagnosis is sometimes in doubt even after an autopsy because the patient’s prolonged stay on a mechanical ventilator in a state of vascular compromise leads to artifactual changes in multiple organ systems.

Pathological Findings

Dr. Mezger:
The cause of death at autopsy was considered to be Reye’s syndrome, and as Dr. Sarnaik said, the findings, even at autopsy, are not always specific. Reye’s syndrome is defined as encephalopathy associated with fatty degeneration of the liver.

The autopsy revealed that the infant was not jaundiced, weighed 13 lbs, and his skin turgor was good. His lungs showed patchy atelectasis, a few focal hemorrhages, and minimal mononuclear inflammatory infiltrates in the bronchi. The heart was microscopically normal, with no change in the cardiac muscle.

The child has a prepyloric ulcer about 2 cm in diameter with a necrotic base, which contained broad nonseptate hyphae consistent with one of the phycycomyce molds, such as Rhizopus, Mucor, or Absidia. These fungi are often associated with metabolic acidosis. We see them most commonly in patients with diabetic acidosis who develop
sinusitis or retro-orbital infections. Blood vessel invasion is common but was not present here.

The liver was moderately enlarged and yellow. Microscopically, it showed the characteristic small droplet fatty degeneration described in Reye's syndrome, although there was no particular distribution to this fatty change (Fig. 1). There was centrallobular necrosis consistent with prolonged anoxia and vascular shock. Inflammatory changes in the liver were not seen. An Oil Red O stain for fat was positive.

The kidneys were swollen, and the proximal tubules showed marked cloudy swelling. No fat was demonstrated in the proximal convoluted tubules with the Oil Red O stain.

The brain was soft and autolyzed, which is consistent with the prolonged stay on the respirator, although severe cerebral edema may also be found in Reye's syndrome. There were no gross localized lesions. Microscopically, there was marked edema and congestion; most cortical neurons had disappeared (Fig. 2). The internal granular layer of the cerebellum showed a loss of Purkinje cells (Fig. 3). Farther down the brain stem and spinal cord, there was progressively less neuronal damage, and the anterior horn cells of the spinal cord were intact. The pattern of neuronal loss was that of hypoglycemia or anoxia, rather than that of vascular loss. The most notable characteristic of the edema was that it was very severe, but no different from what one sees adjacent to abscesses or to brain tumors, or in other neurologic lesions. No inflammation was present in the brain.

The pathology was associated with hypoglycemia, elevated liver and muscle enzymes, and depression of blood clotting factors. Of possible pathogenic significance in Reye's syndrome is the elevated blood ammonia. Elevations of the short chain and medium chain fatty acids have also been reported. When injected into rats, these free fatty acids have caused disease similar to Reye's syndrome associated closely with mitochondrial damage, as demonstrated by electron microscopy. Liver biopsy examinations of patients with Reye's syndrome have also demonstrated prominent swelling of mitochondria, which is reversible as the patient recovers. The mitochondria are factories of the liver, the organs in which the enzymatic processes of the liver are controlled. Damaged mitochondria disturb enzyme function and alter metabolism.

We don't know much about the etiology of Reye's syndrome. The primary injury probably occurs in the liver and leads to mitochondrial damage and to liver dysfunction. This damage produces a deficiency of various enzyme systems, the urea cycle enzymes, the enzymes of glucose metabolism, and those that regulate the tricarboxylic acid cycle. As a result, blood ammonia and free fatty acids
increase, and hypoglycemia occurs. Now whether this damage is due to a toxin, a virus, or some kind of immune complex disease we don’t know. The hypoglycemia and other metabolic changes lead to cerebral anoxia and edema that cause death.

Questions

How were the muscles involved?

Dr. Mezger:
The myocardium was not involved. No skeletal muscle sections were taken.

Doesn’t the age group of Reye’s syndrome patients present a problem in describing the brain? Generally, you can’t section the brain of children who die from Reye’s syndrome because it’s just a mush.

Dr. Mezger:
Yes, that is correct. This child was on the respirator for several days and the brain was practically a mush, even though well fixed when cut.

Dr. Shobha Sahney:
Kidneys have been harvested from children who have died from Reye’s syndrome, and when they are used as donor kidneys for transplants, they have done very well. So with patients with Reye’s syndrome, we should look to them as kidney donors if they have stable blood pressure, and all vital signs remained stable on the respirator.

I’d like to ask Dr. Sarnaik about his experience with Reye’s syndrome at Children’s Hospital. You see a tremendous number of cases, about 30 a year. I would like to know how you are treating your patients now.

Dr. Sarnaik:
Although we see about 30 cases a year, the incidence has a marked seasonal variation. Most cases occur in October and November through March. Most patients are between five and 15 years old. In an infant like the child presented today with encephalopathy, and some liver dysfunction, I am very cautious about making a diagnosis of Reye’s syndrome. Several infants have been referred to us with the diagnosis of Reye’s syndrome who turned out to have other illnesses, such as salicylate intoxication, meningitis, viral encephalitis, and inborn errors of metabolism. Many times the diagnosis of Reye’s syndrome in infancy is an admission of our ignorance. The syndrome as originally described by Reye is a clinicopathological entity; several illnesses can probably be classified as Reye’s syndrome. I think we should restrict this diagnosis to an illness with a typical course that presents with viral infection, vomiting, and onset of encephalopathy.

The management of Reye’s syndrome is predominantly supportive. The ability of the clinician to control intracranial pressure and to protect the brain from irreversible injury due to pressure and ischemia determines the child’s ultimate survival. Some reports have mentioned that Reye’s syndrome occurred without raised intracranial pressure, but the vast majority of critically ill patients will have intracranial hypertension. In the early stages of encephalopathy, the child may be lethargic but is oriented in time, space, and person. There may be some mental confusion or loss of verbal spontaneity. Our management of these children is restricted to intravenous glucose administration to prevent hypoglycemia and fluid restriction to 1500 ml/m². Occasionally, an osmotic diuretic such as Mannitol may be needed. Steroids are used in intracranial hypertension from other causes such as trauma, but we are not very impressed with their usefulness in Reye’s syndrome.

The cerebral edema of Reye’s syndrome is predominantly cytotoxic, so that the cells themselves are swollen. Idiogenic osmols are produced; no one knows what they are, but they cause the cells to swell. Osmotic diuretics are used to decrease intracellular water content.

As encephalopathy progresses, the patient starts assuming characteristic decorticate posture with flexion of the upper extremities and extension of the lower extremities, or decerebration on painful stimuli. Verbal stimulation produces no purposeful response. At this stage we use intracranial pressure monitors. According to the clinical state and the intracranial pressure, osmotic therapy is used. We try to keep intracranial pressures to less than 20 mm Hg, the normal being somewhere between 5-12 mm Hg. Intracranial pressure over 20 mm Hg is treated aggressively with Mannitol, Pentobarbital, and mechanical ventilation. Patients at this stage of severity are intubated and mechanically ventilated to keep PaCO₂ around 25 Torr.

Until several years ago we were faithfully doing exchange transfusions in these patients. I do not think there is any good evidence that exchange transfusions are beneficial, although in a few patients the intracranial pressure drops and the encephalopathy improves. We have largely given up the routine use of exchange transfusions, except in a few selected cases when the use of Mannitol produces hyperosmolality. One has to be sure of adequate renal function when Mannitol is used, because if renal function is impaired, Mannitol may cause hyperosmolality, hyper-

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volemia, and worsening of encephalopathy. These patients are also monitored with central venous pressure and arterial catheters. We like to keep the cerebral perfusion pressure (mean arterial blood pressure-intracranial pressure) over 50 mm Hg. As Dr. Sahney mentioned, most of the organs involved in Reye's syndrome, the liver, kidney, heart, and even the brain, can recover completely if the patient can be supported for a period of time.

The neurological outcome of patients with Reye's syndrome is very encouraging. Our major challenge is to save these children at all costs because their brain is going to recover completely in most cases. Our neurological follow-up shows that the intelligence of patients who survive severe Reye's syndrome is spared quite well. They may have temporary cognitive defects but their IQs are satisfactory (8).

References