REYE'S SYNDROME
DIAGNOSTIC and THERAPEUTIC
CONSIDERATIONS:
The Importance of Early Diagnosis

By James E. Heubi, M.D.

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Reye's Syndrome—Diagnostic and Therapeutic Considerations: The Importance of Early Diagnosis

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Table 1
Clinical Staging of Reye's Syndrome

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Quiet, responds to commands</td>
</tr>
<tr>
<td>2</td>
<td>Lethargic, stuporous, thick speech</td>
</tr>
<tr>
<td>3</td>
<td>Agitated delirium, intermittently out of contact with environment</td>
</tr>
<tr>
<td>Severe</td>
<td>Coma; decorticate/decerebrate posturing, hyperpnea, hyperpyrexia</td>
</tr>
<tr>
<td>4</td>
<td>Coma, flaccid paralysis</td>
</tr>
</tbody>
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CLINICAL SIGNS AND LABORATORY FINDINGS IN TYPICAL CASES OF REYE'S SYNDROME:

1) Typically, the child will initially have an uncomplicated upper respiratory illness (cough, rhinorrhea, fever) and malaise. As the illness progresses, vomiting begins. Low grade fever may be present but is usually absent. The vomiting begins, the progression of sensorial changes (Table 1) is variable. Some patients have no change in consciousness and remain only lethargic to variable degrees (Grade I and II) with no progression to unconsciousness. These patients appear destined to recover uneventfully. A small number of patients will progress to a hyperirritable state (agitated delirium) during which they become disoriented and have screaming episodes (Grade III). Further progression to deep coma states characterized by decorticate and decerebrate posturing with hyperventilation and hyperpyrexia (Grade IV) and finally flaccid paralysis with loss of voluntary ventilatory control (Grade V) may be slow or rapid. What controls the rate of progression is unknown at present. Seizure activity is rare in mildly affected patients but may occur during deeper grades of coma. The encephalopathy typically persists for 24-96 hours and gradual improvement in neurologic function occurs in sur-

In 1963, Reye, Morgan and Baral described the clinical and pathologic features of 21 Australian children with what is now broadly recognized as Reye's Syndrome. Almost simultaneously Johnson, Scurtis and Carroll described the same clinicopathologic findings in 16 North Carolina children. In both series, high mortality rates were observed associated with vomiting, progressive coma and fatty infiltration of the viscera. Over the ensuing 19 years, at least 2000 cases have been reported to the Center for Disease Control. Although the specific cause of the dis-

Figure 1: Adapted and reprinted with permission from Panos JC. Hepatic encephalopathy and Reye's Syndrome. Ped Am Ass May 1977
Table 2
Laboratory Features of Reye's Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Non-Comatose</th>
<th>Comatose</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>100-3000 IU</td>
<td>400-3000 IU</td>
<td>8-30 IU aca</td>
</tr>
<tr>
<td>SGPT</td>
<td>100-3000 IU</td>
<td>400-3000 IU</td>
<td>3-30 IU aca</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;1 mg/dl</td>
<td>&lt;1 mg/dl</td>
<td>&lt;1 mg/dl</td>
</tr>
<tr>
<td>NH₃</td>
<td>20-200 μg/dl</td>
<td>100-1000 μg/dl</td>
<td>&lt;48 μg/dl</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>10.0-14.0 seconds</td>
<td>13-16 seconds</td>
<td>9.6-11.9 seconds</td>
</tr>
<tr>
<td>CPK</td>
<td>50-200</td>
<td>50-1000</td>
<td>&lt;110 IU aca</td>
</tr>
<tr>
<td>Salicylate</td>
<td>1.0-30.0</td>
<td>1.0-30.0</td>
<td>&lt;1.7 mg/dl</td>
</tr>
</tbody>
</table>

For signs of progression since only subjects with such increases in NH₃ concentrations have progressed in the Cincinnati series. The serum glucose may be normal but frequently is reduced in infants and normalizes with intravenous fluid therapy. The serum bilirubin rarely exceeds one mg/dl at presentation unless superimposed shock is present. The prothrombin time (PT) is usually only modestly prolonged (one to three seconds over control) but occasionally significant prolongation is present (three to 10 seconds over control). The PT generally normalizes in three to five days with the aid of parenteral vitamin K. The creatine phosphokinase (CPK) may be moderately to markedly increased. The serum electrolytes are generally normal; however, BUN and creatinine may be mildly elevated indicative of mild dehydration. Cerebrospinal fluid findings include fewer than eight white cells/mm³ with normal protein and glucose concentrations. If hypoglycemia is present, reduced spinal fluid glucose concentrations may be present.

A percutaneous liver biopsy will confirm the diagnosis of Reye's Syndrome. Grossly the biopsied liver is pale or yellow instead of the normal tan or brown color. The liver histology, histochemistry and ultrastructure have typical and specific features in Reye's Syndrome. Examination of hematoxylin-eosin stained sections reveals normal or swollen hepatocytes with centrally located nuclei, insignificantly increased inflammation, rare cellular necrosis and no cholestasis (Figure 2a). Lipid histochemical studies on frozen sections using oil red O or Sudan Black stains reveal abundant small droplet fat in hepatocytes in a panlobular distribution (Figure 2b). Histochemistry studies of mitochondrial enzymes (succinic acid dehydrogenase) allow demonstration of a variable reduction in enzyme activity in the lobule with some activity remaining in the perportal areas (Figure 2c). In contrast, similar studies of cytosolic enzyme (DPNH) activity demonstrate normal activity. The mitochondrial alterations, which have been considered to be the hallmark of the hepatic pathology, include matrix expansion, loss of matrix density and dense bodies and irregularities of the limiting membrane (Figure 2d). Additional ultrastructural findings include lipid accumulation, glycogen depletion and increases in the number of peroxisomes.

**Differential Diagnosis**

The differential diagnosis of Reye's Syndrome, in part, is dependent upon the age of the patient and the presence or absence of coma. The clinical diagnosis of Reye's Syndrome in older subjects can be readily made when multiple criteria are present including 1) a prodromal illness, 2) acute onset of encephalopathy after protracted vomiting, 3) SGOT/SGPT elevation at least three times normal with normal serum bilirubin concentrations or the presence of histologic changes consistent with Reye's Syndrome at biopsy or autopsy, 4) absence of cerebrospinal fluid pleocytosis and 5) absence of another reasonable explanation. The sequence of events in which a prodromal illness followed by vomiting, serum transaminase elevation and hyperammonemia with development of agitated delirium and coma are fairly stereospecific for Reye's Syndrome (Table 3).

**Table 3**
Diagnostic Criteria for Reye's Syndrome

1. Prodromal viral illness (usually URI or chicken pox).
2. Onset of persistent vomiting three to seven days after prodrome with or without change in sensorium.
3. SGOT/SGPT at least 3x normal with normal or elevated serum ammonia and no jaundice.
4. Cerebrospinal fluid containing ≤ 8 WBC/mm³.
5. Microvesicular fatty metamorphosis of the liver (not essential in facilities where biopsies not available or during outbreaks of Reye's Syndrome).
6. No other reasonable explanation for the illness.

For infants less than one year who are generally significantly encephalopathic (Grade III or IV), consideration must be given to inborn errors of metabolism. Hypoglycemia or hepatic encephalopathy may prompt medical attention in infants with galactosemia, hereditary fructose intolerance, or even glycogen storage disease; however, serum bilirubin may be elevated in the former two conditions and hepatomegaly is a prominent feature of all. Infants with systemic carnitine deficiency may present with Reye's-like symptoms with hepatomegaly, acidosis and SGOT/SGPT elevation. Urea cycle enzyme deficiencies (specifically ornithine transcarbamylase and carbamyl...
phosphate synthetase) may result in profound hyperammonemia and encephalopathy with minimal hepatomegaly and minimal SGOT/SGPT elevation. Similarly, patients with isovolemic acidemia or other organic acidemias may present with acidosis and encephalopathy without evidence of hepatic dysfunction.

For comatose patients of all ages, meningitis, viral encephalitis, toxin or drug induced coma (especially salicylate), hypoxic encephalopathy and anoxic liver damage, cerebrolobar necrosis with shock and encephalopathy, and fulminant hepatic failure due to hepatitis must be excluded. In most of these circumstances, historical facts and additional laboratory investigations (as indicated by history) can effectively satisfy the practitioner that these conditions are not present.

For non-comatose patients, the differential diagnosis includes a smaller number of conditions. Anicteric hepatitis A or B, Ebstein-Barr viral hepatitis, cytomegaloviral hepatitis, varicella hepatitis and drug-induced hepatitis (aspirin or acetaminophen) may mimic Reye's Syndrome. All of the above conditions can be excluded by appropriate serologies, serum drug levels and close attention to the history of the antecedent prodromal illness. Even physicians experienced in identifying Reye's Syndrome have difficulty differentiating many of the above conditions from biopsy-proven Reye's Syndrome. Especially difficult is the situation in which a patient is receiving aspirin for management of arthritis in which nausea, vomiting, and lethargy supervene. In these circumstances, the serum salicylate concentration is within the therapeutic and potentially hepatotoxic range. At present the only way to differentiate aspirin-induced hepatotoxicity from Reye's Syndrome is by percutaneous liver biopsy. In non-progressive cases, the importance of this differentiation may be moot since most parents refuse future aspirin use after such an episode.

Etiology

The causes of Reye's Syndrome remain unknown despite many years of study. The relationship between Reye's Syndrome and antecedent prodromal illnesses has been long recognized. In most large studies of Reye's Syndrome, upper respiratory illnesses account for the prodrome in approximately 60% of cases, varicella in 30% and diarrheal illnesses in 10%. Multiple viral agents including mumps, coxsackie, Ebstein-Barr, Echo, influenza A and B and varicella have been associated with it. Of the implicated viral agents, influenza A and B and their relationship to Reye's Syndrome have been most thoroughly examined. During epidemics of influenza A and B in 1973-74, 76-77, 77-78, 79-80 and 80-81, a temporal relationship between reported Reye's cases and influenza cases has been recognized (Figure 3). Varicella prodromal Reye's Syndrome tends to be more sporadic during the winter-spring periods and an epidemiologic link to Reye's Syndrome seems clear.

It has been suggested by several investigators that there may be synergistic relationships between exogenous toxins, viral infections and the development of Reye's Syndrome. Aflatoxin, insecticides, and hypoglycin have all been implicated as exogenous toxins which might lead to the development of Reye's Syndrome or illnesses mimicking it. Hypoglycin is a toxin found in the unripe fruit of the ackee tree and is the etiologic agent in Jamaican vomiting sickness. Hypoglycin is a chemical analogue of 4- pentenoic acid, a short chain fatty acid which may produce profound alterations in consciousness in experimental animals. Recent studies by Tanaka et al., suggest substantial differences in serum and urinary organic acid levels between Reye's Syndrome and Jamaican vomiting sickness. Aflatoxins represent toxic metabolites of Aspergillus flavus and have been implicated in Reye's Syndrome-like illnesses in Thailand. However, hepatic histology in affected patients is substantially different from Reye's Syndrome. More recent work by Crocker et al., has suggested a link between pesticide exposure and Reye's Syndrome through their observations of lethal fatty infiltration in the liver associated in an animal model exposed to a viral-pesticide emulsifying agent combination.

Although the above viral-toxin combinations represent interesting suggestions as to the cause of Reye's Syndrome, inadequate evidence is currently available to implicate them as the cause of Reye's Syndrome. Abnormalities of short chain fatty acid and ammonia metabolism have been suggested as etiologic in Reye's Syndrome, however, abnormalities in metabolism of these substances are reversible with recovery. In addition, the low familial incidence of Reye's Syndrome and low recurrence rates suggest that hereditability is often absent. More re-
cently, epidemiologic studies in Ohio, Michigan and Arizona have suggested an
etiologic link between aspirin usage and Reye's Syndrome. In each of these three
case-control studies, a significantly larger number of children who developed Reye's Syndrome had antecedent exposure to aspirin than their case controls. Additional
similar observations regarding aspirin usage and Reye's Syndrome have been
made since the identification of the disease entity in 1963. At Children's Hospital in
Cincinnati elevated serum salicylate concentrations and antecedent exposures are
commonly observed. Partin et al. found that 95% of 64 patients with Reye's Syndrome had antecedent aspirin exposure compared to 80% of controls with URI and the estimated aspirin ingestion during the illnesses was twice as high in Reye's patients. They further observed that salicylate concentrations in Reye's patients (n=27) were almost 10 times those in the URI controls; however, they found no correlation between serum salicylate levels and neurological grade of the Reye's patients on admission. None of these studies prove a cause and effect relationship between aspirin use and Reye's Syndrome; however, they suggest that it may be a co-factor with an antecedent viral illness and as yet undetermined host and other factors which by synergism result in the development of Reye's Syndrome. Since a small number of patients develop Reye's Syndrome without antecedent salicylate usage, its use cannot be categorically construed as a necessary ingredient in the pathogenesis of the disease.

Epidemiologic and Demographic Considerations

Reye's Syndrome may affect infants, children and adolescents. Few cases have been described in adults. The average age of presentation at Cincinnati is seven years. Males and females are equally affected. The illness is found predominantly in white children and is relatively uncommon in blacks. A rural/suburban/urban distribution of the geographic origin of cases has been well recognized.

The exact frequency of the disease remains unknown. The Center for Disease Control (CDC) has suggested that the incidence of Reye's Syndrome is 0.3-0.9 cases per 100,000 children less than age 17 years. The CDC has also suggested that the incidence may be three to four cases per 100,000 cases of influenza B in children. Geographic variability in the reported incidence of disease is well recognized.

Pacific states have consistently low rates of reported cases while several mountain, West North Central and East North Central States have consistently high rates. It remains unclear why differences in distribution exist; however, differences in influenza activity, environmental or cultural factors may play significant roles. Recent studies from Cincinnati (where there is a high community and physician awareness of the disease and its manifestations) suggest that the CDC estimate of Reye's Syndrome incidence underestimates the true frequency of the disease. In a prospective study from December 1, 1980 to November 30, 1981, the incidence of biopsy-proven Reye's Syndrome in the Cincinnati metropolitan area was 3.1 cases per 100,000 children under age 17 years. It is likely that this incidence figure is an underestimate because additional non-comatose cases may have never arrived at the hospital for evaluation and treatment. The majority (75%) of cases identified in our study were non-comatose suggesting that the incidence figures previously reported by the CDC most likely represent the "tip of the iceberg" with a large number of non-comatose patients unrecognized in the community and therefore unreported.

Treatment

Early recognition, before the development of serious neurologic signs, results in a better outcome than any treatment currently available for Reye's Syndrome. All physicians and nursing personnel (especially in emergency rooms, clinics and private offices) should be familiar with cardinal presenting symptoms of Reye's Syndrome. Reye's Syndrome should be suspected in any child with chicken pox who repetitively vomits. Careful questioning of parents regarding an antecedent prodromal illness in any patient with unexplained persistent vomiting with or without obtundation should be routine. It is also important to remember that significant fever (101°F) and diarrhea are rare at the onset of emesis in Reye's Syndrome. Any patient with persistent vomiting with an antecedent respiratory infection or chicken pox within the preceding week should have a physical examination and an SGOT or SGPT determination. If the patient has SGOT/SGPT elevation greater than three times normal with or without neurologic symptoms, the patient should be admitted to the hospital for careful observation, treatment with intravenous fluid containing 10% glucose, 40-60 mEq/m²/day sodium and 40-60 mEq/m²/day potassium at a rate of 1500-1800 cc/m²/day with cautious correction of dehydration (Table 4). Additional laboratory measurements including total serum bilirubin, prothrombin time, plasma ammonia, blood glucose, electrolytes, BUN, serum salicylate, serum and urine toxic screen and appropriate serologies should be obtained to exclude the presence of hepatitis A or B, Epstein-Barr virus and cytomegalovirus. The question of whether a lumbar puncture should be obtained should be based upon the physician's clinical judgment. The necessity of a liver biopsy to establish the diagnosis of Reye's Syndrome in non-comatose patients remains debatable. Although the risk of complication from biopsy is low, a liver biopsy need not be performed unless active studies regarding non-comatose cases are ongoing (as they are in Cincinnati). It appears that in most mild cases of Reye's Syndrome, even the trivial risk of percutaneous liver biopsy is unjustified because the benefits appear diminishingly small.

The majority of non-comatose patients will not progress to deeper coma grades with conservative expectant therapy. The vomiting will stop, the appetite will return and the patient is usually discharged from the hospital in 48-96 hours after admission. A small number of non-comatose patients will progress and require more intensive care (see below). At Cincinnati, we have had the opportunity to observe the clinical course of over 75 biopsy-proven Grade I Reye's Syndrome patients. Our experience suggests that only 5% progress to deeper neurologic grades and none die if they are treated by the means described here. It remains unclear to us if this mode of therapy truly aborts the progression of disease; how-

| Table 5 |
| Treatment of Reye's Syndrome (Comatose) |
| 1. Begin intravenous 10% glucose/electrolytes at 1200-1500 cc/m²/day. |
| 2. Undertake intensive nursing and physician care. |
| 3. Start Vitamin K, 5 mg (either slowly IV or IM). |
| 4. Maintain airway and avoid anoxia. |
| 5. Monitor urine flow and correct electrolyte disturbances. |
| 6. Start continuous intracranial pressure and mean arterial pressure monitoring to maintain cerebral perfusion pressure above 50 mm Hg. |
| 7. Consider early elective endotracheal intubation and controlled ventilation. |
| 8. Treatment for intracranial hypertension a. Initiate hyperventilation to keep pCO₂ between 20-25 mm Hg. b. Administer mannitol 0.5 gm/kg over 30 minutes q4-6 hours. c. Administer pentobarbital 3-5 mg/kg initially and 2-3 mg/kg hourly to maintain barbiturate level at 2.5-4.0 mg/dl. |

| Table 4 |
| Treatment of Reye's Syndrome (Non-comatose) |
| 1. Early recognition |
| 2. Intravenous 10% glucose/electrolyte at 1500-1800 cc/m²/day |
| 3. Expectant observation in hospital |
ever, we are unwilling to recommend observation of mild Reye’s Syndrome patients at home for fear that they may have a higher risk of progression without therapy and an attendant higher morbidity and measurable mortality.

If the child is comatose (greater than Grade II), a lumbar puncture with examination of the cerebrospinal fluid for cell count, total protein and glucose is mandatory to exclude the presence of infection. All comatose patients should be hospitalized in an intensive care setting in which there is not only 24-hour nursing care but also readily available (in-house) physician coverage (Table 5). Intraventricular fluids should be administered as 10% glucose/electrolyte solutions at 1200-1500 cc/m2/day. Urine output, specific gravity and compliance should be monitored using an indwelling Foley catheter. Vitamin K, 5 mg parenterally, should be given and a percutaneous liver biopsy performed to confirm the diagnosis of Reye’s Syndrome. All cases should have intracranial pressure (IP) monitoring, by any of one multiple available methods (intraventricular cannula, subarachnoid bolt or epidural transducer). It is also wise to simultaneously have continuous arterial pressure monitoring through an indwelling arterial access line to measure mean arterial pressure (MAP). By having simultaneous measurements of both, one can ensure that adequate cerebral perfusion pressure (CPP) is maintained. In this situation, CPP = MAP – IP and should optimally exceed 50 mm Hg (1 mm Hg = 1.36 cm H2O). To expect this optimum, close attention must be paid to maintenance of a patent airway and adequate oxygenation. Early elective endotracheal intubation is wise in most comatose cases and is usually performed at the time the intracranial pressure monitor is inserted. Administration of paralyzing agents (Pavulon®) may be necessary to allow effective ventilation. A cooling blanket should be used if necessary to maintain normothermia. Aggressive therapy directed at treatment of intracranial hypertension should be initiated when ICP exceeds 20 mm Hg or the CPP is less than 50 mm Hg. Initial therapy should include mechanical hyperventilation to allow a reduction in the pCO2 to 20-25 mm Hg. Cerebral dehydrating agents are also useful in reducing increased intracranial pressure and should be utilized next. Mannitol in doses of 0.25-1.0 g/kg q4-6 hours given intravenously over 30 minutes has been effective. The use of glycerol has not proved additive in our hands and has not been as effective as mannitol. Dexamethasone is not useful in the treatment of cerebral edema of Reye’s Syndrome. If the patient has uncontrollable intracranial hypertension despite the above measures, barbiturate therapy should be considered. The initial dose of pentobarbital should be 3-5 mg/kg with subsequent hourly doses of 2-3 mg/kg to maintain a blood barbiturate level of 2.5-4.0 mg/dl. If the mean arterial pressure declines so that the cerebral perfusion pressure is compromised or the blood barbiturate level exceeds 4 mg/dl, doses should be withheld. In selected cases in whom all modes of therapy appear ineffective in controlling intracranial hypertension, decompressive craniectomy may be life-saving. This drastic approach may be useful in selected circumstances but requires proctorization (once you decide on this course of action) may mean the difference between a favorable and unfavorable neurologic outcome. No specific guidelines are available for selection of appropriate candidates for this treatment modality. Additional treatment modalities including exchange transfusion, peritoneal dialysis and total body washout are largely of historical interest and do not offer any additional advantage over the above outlined protocol.

Outcome

The nationwide case fatality rate reported to the Center for Disease Control from 1973 to 1981 has declined from 40% to 25%. It is evident that the case fatality rate is dependent upon the admitting grade of coma and the highest grade of coma during the course of the illness. This can be graphically illustrated by the fact that the mortality rate of Reye’s Syndrome for all cases admitted to Children’s Hospital in Cincinnati is 3%. No cases of Reye’s Syndrome admitted who were neurologic Grade I have died at Cincinnati and minimal morbidity has occurred in this group. This finding suggests that early recognition may essentially eliminate the significant morbidity of Reye’s Syndrome. No mortality has been observed with patients with Grade II neurologic findings on admission. A progressive decline in survival has been observed in deeper coma grades with an overall mortality of 25% in patients admitted in Grade III, 35% in Grade IV and 50% in Grade V. While noted in Grade III, 5% of patients admitted in Grade III have died, 25% admitted in Grade IV coma have died and all patients admitted in Grade V have died. Follow-up neuropsychological examinations in survivors of Reye’s Syndrome have suggested that comatose (Grade III + IV) survivors may have a variety of sequelae ranging from evident psychomotor retardation with overt neurologic deficits to more subtle perceptual abnormalities. Work by Brunner et al. from Cincinnati supported the clinical observations that the neuropsychological consequences paralleled disease severity. Their work also suggested that recovery from the neuropsychological impairments may transpire over many months after recovery from Reye’s Syndrome. Additional clinical observations have suggested that the prognosis both in terms of mortality and neuropsychological impairment is considerably worse for infants less than age one year than in older patients.

Concluding Remarks

Early detection is the key to effective management of Reye’s Syndrome. Physicians, nurses and parents should be aware of the cardinal features of Reye’s Syndrome. Many communities like Cincinnati have mounted massive efforts to educate parents about the signs of Reye’s Syndrome. Materials available for this purpose may be obtained through the National Reye’s Syndrome Foundation, P.O. Box 829, Bryan, Ohio 43014. It is equally important for us to educate new physicians and older community physicians regarding this disease so that prompt, effective and potentially life-saving therapy may be initiated.

References