30. The Diagnosis and Treatment of Reye's Syndrome

[THIS STATEMENT IS NO LONGER VIEWED BY NIH AS GUIDANCE FOR CURRENT MEDICAL PRACTICE.]

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Introduction

A Consensus Development Conference was held at the National Institutes of Health on March 2, 3, and 4, 1981, to address issues on the diagnostic criteria and treatment of Reye's syndrome.

At NIH, consensus development conferences bring together investigators in the biomedical sciences, practicing physicians, consumers, and advocate groups to provide a scientific assessment of technologies, including drugs, devices, and procedures, and to seek agreement on their safety and effectiveness.

On the first two days of the meeting, a consensus development panel and members of the audience reacted to evidence presented on the following questions:

- What are the key signs, symptoms, and laboratory findings of Reye's syndrome?
- What is the evidence for the effectiveness of the various treatments of Reye's syndrome?
- What are the clinical and experimental studies needed to advance our ability to diagnose and treat Reye's syndrome?

The members of the panel represented the disciplines involved in the diagnosis and treatment of those with Reye's syndrome. Panelists were nominated by seven specialty associations: the
American Academy of Neurology, the American Academy of Pediatrics, the American Association of Neurological Surgeons, the American Society of Anesthesiologists, the American Academy of Family Physicians, the Child Neurology Society, and the American Nurses Association. This summary is the result of the panel's deliberations.

Reye's syndrome is a life-threatening illness that affects children of all ages, with a peak incidence between 5 and 15 years; on rare occasions it has been reported in adults. Although Reye's syndrome (encephalopathy with fatty degeneration of viscera) has been extensively investigated since the classic description of the disorder by Reye, Morgan, and Baral in 1963, the etiology and pathogenesis of this disease process remain obscure. The subcellular insult appears to affect mitochondria in multiple organ systems. Since prompt treatment may provide a better chance for complete recovery, early diagnosis is important.

Dissemination of information on the early symptoms of Reye's syndrome, diagnostic criteria, and essential aspects of therapy is recommended. Such information should be distributed to parents, physicians, and nurses to facilitate early recognition, diagnosis, and treatment.

What Are the Key Symptoms?

Reye's syndrome should be suspected in a child who, during or while recovering from a viral illness (most commonly chicken pox or influenza), unexpectedly develops repetitive vomiting and altered behavior such as lethargy, confusion, irritability, or aggressiveness. Neither fever nor jaundice is usually present. In children under one year of age, respiratory disturbances such as hyperventilation or apneic episodes may be prominent. In this special group (<1 year old) seizures occur more frequently than in older patients. All children with the above pattern of illness should receive prompt medical attention.

What Are the Laboratory Findings in Reye's Syndrome?

Helpful laboratory tests include the level of transaminases in serum, ammonia concentration in blood, and prothrombin activity. The activity of serum transaminases is at least three times upper normal limits, prothrombin time is usually prolonged, and blood ammonia concentration is usually elevated. Jaundice is conspicuously absent and bilirubin levels rarely are elevated. The concentration of glucose in blood is usually normal, especially in children 4 years of age and older. The cerebrospinal fluid (CSF) usually contains fewer than 8 cells per mm^3 and normal protein and glucose concentrations, except when there is concomitant hypoglycemia. Other recommended laboratory tests include determination of the concentration of glucose, calcium, and phosphorus in blood and of serum amylase activity. Serum should be analyzed for levels of salicylate and acetaminophen.
**Where Should a Patient Be Treated?**

It is most important that primary care practitioners be highly aware of Reye's syndrome and perform appropriate laboratory investigations promptly. Children with a history and laboratory findings suggestive of Reye's syndrome should be hospitalized for careful observation and receive glucose by intravenous infusion. Patients with Stage II* symptoms or worse should be cared for in a pediatric intensive care unit by a multidisciplinary team according to an established protocol, when available.

* Stages in this paper refer to those described in Table 1.

If the diagnosis of Reye's syndrome is made in a primary care setting, the physician should consult with colleagues in a pediatric intensive care center and discuss the timing of transfer. The transport team should be prepared to provide support for vital functions.

**What Are the Currently Used Rating or Classifying Systems for Measuring the Severity of Clinical Symptoms? How Useful Are They?**

A variety of staging systems based upon neurologic findings have been proposed for Reye's syndrome which have proven useful in assessing the severity of the illness, monitoring the effect of therapy, and predicting ultimate outcome. The multiplicity of staging systems, however, has been confusing for clinicians and researchers alike.

**Should a Uniform System Be Recommended for General Use?**

The panel reviewed a number of proposed staging systems and recommends the system outlined in Table 1 for future use in management and study of Reye's syndrome. Patients with high concentrations of ammonia in blood early in the course of disease appear to have a less favorable prognosis.

**Table 1 - Staging of Reye's Syndrome**

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* NIH Consensus Statements: 30. The Diagnosis and Treatment of Reye's Syndrome*
### When is a Liver Biopsy Needed?

The diagnosis of Reye's syndrome can be made in most patients without a liver biopsy, a procedure not to be undertaken lightly in an uncooperative, critically ill child with defective coagulation. The results may confuse rather than inform unless the tissue is processed and interpreted by personnel in a center with special knowledge of the illness.

Nevertheless, a carefully planned biopsy, after correction of the coagulation abnormality, carried out by physicians experienced in performance and interpretation of the results of such biopsies, can provide important information in certain specific situations. Biopsy should be considered in: (l) infants, (2) children with recurrent episodes, (3) familial cases, and (4) nonepidemic (sporadic) cases without antecedent infection or vomiting. Biopsy also increases the certainty of diagnosis and is important if a new and potentially dangerous therapeutic regimen is planned.

### What Other Conditions May Present With Similar Symptoms?

There is a lengthening list of illnesses that may be temporarily misidentified as Reye's syndrome. We now recognize that transaminase elevations may occur in children with varicella without Reye's syndrome and in shock or hypoxia due to a wide variety of illnesses. Intramuscular injections (especially of a commonly used antiemetic, chlorpromazine) and protracted seizures may increase levels of transaminases in serum in a variety of diseases which affect the central nervous system. Methyl bromide, hypoglycin (senecio alkaloid), isopropyl alcohol, folk remedies (pyrrolizidine and margosa oil), aflatoxin, lead, and toxicity from some drugs (e.g., aspirin, acetaminophen, and valproic acid) may produce disturbances...
of consciousness and elevation of serum transaminases.

When confronted by familial or recurrent episodes of Reye-like illness, the physician should consider an inborn error of metabolism, especially systemic carnitine deficiency, glutaric acidemia, ornithine transcarbamylase deficiency, or hereditary fructose intolerance.

What Special Diagnostic Tests Are Needed?

Computerized transaxial (CT) brain scanning is neither necessary nor indicated for diagnosing Reye's syndrome unless there is clinical suspicion of a disease other than Reye's syndrome, e.g., subdural hematoma, brain abscess, etc. Thus, CT scanning is not an integral part of the diagnostic evaluation of the child with Reye's syndrome. If, however, the test is done early in the course of illness, it will show either a normal pattern or evidence of diffuse brain edema, with no displacement of the ventricles or localized areas of enhancement.

The usefulness of electroencephalography (EEG) depends on the availability of appropriate equipment and individuals skilled in EEG interpretation. In general, the EEG has not proved to be helpful in following patients, determining prognosis, or altering treatment.

What Have Been the Indications for Intracranial Pressure Monitoring? What Devices Are Available? What Are the Goals in Reducing Intracranial Pressure And when Can Monitoring Be Stopped?

Since 1975, several reports have suggested that invasive monitoring of intracranial pressure may be useful in the management of children with Reye's syndrome. The devices in use can provide continuous measurement of pressure in the epidural, subarachnoid, or ventricular spaces. The difficulties inherent in assessing the usefulness of this procedure, employed to monitor rather than to treat, have produced conflicting opinions. Some physicians believe it improves their ability to manage patients, others do not. Mortality and morbidity directly attributable to monitoring devices appear to be low in the medical centers where they are used frequently. Data are inconclusive regarding criteria for discontinuation of such monitoring.

What Are Appropriate Therapies in the Noncomatose Patient?

Therapy for Stage I patients includes administration of dextrose-containing fluid. While there are no studies documenting that glucose administration in excess of that provided by 5
percent glucose solution at maintenance rate is definitely beneficial, a number of considerations have prompted many clinicians to administer 10 percent dextrose solutions to these mildly affected children. If neurologic deterioration occurs, the rate of fluid administration must be adjusted to maintain critical organ perfusion. Episodes of hypotension have been reported with maintenance rates of fluid administration following osmotic diuresis.

For many reasons, hemodynamic monitoring is important. Arterial catheters permit continuous blood pressure measurement and frequent arterial blood-gas sampling. Central venous catheters may provide useful data concerning blood volume and cardiac function, while pulmonary artery catheters (providing measurement of cardiac output) may be helpful in selected seriously ill children. While central venous catheters may be preferable in patients with normal cardiopulmonary function, the management of complicating cardiac dysfunction due to disease or drugs may make more complete monitoring necessary.

Intubation of patients with Reye's syndrome has received general acceptance, although there is disagreement as to what criteria are used to make the decision to intubate. There is agreement that intubation should be elective (i.e., prior to respiratory failure or cardiac arrest). It is most often prompted by deteriorating neurologic progression toward coma and is accomplished with intravenous succinylcholine and barbiturate.

What Are the Important Metabolic Derangements and Are They Amenable To Treatment?

There are many documented metabolic derangements in Reye's syndrome, including hypoglycemia, hyperammonemia, hyperlactatemia, short chain fatty acidemia, hypophosphatemia, hyperaminoacidemia, azotemia, hyperuricemia, elevations of several hormones, and a mixed acid-base disorder. Accepting these well-documented findings and their relationship to the severity or treatment of the disease remain speculative. Although the degree of metabolic perturbation roughly parallels the severity of clinical illness, efforts (dialysis, amino acid infusion, phosphate and insulin infusions) to correct specific metabolic abnormalities have not clearly altered outcome.

Administration of vitamin K is generally accepted, although it is recognized that it is unlikely to correct fully clotting abnormalities. If significant bleeding occurs, exchange transfusion with fresh blood or administration of fresh frozen plasma may be helpful.

What Are the Therapies for Increased Intracranial Pressure?

While the encephalopathy of Reye's syndrome is not always associated with increased intracranial pressure, such elevations frequently complicate the care of patients in coma. In lieu of specific treatment of the encephalopathy, much effort has been directed to the control of increased intracranial pressure. Measures commonly employed include osmotherapy and
spontaneous or controlled hyperventilation. Experimental measures include high-dose barbiturates, corticosteroids, CSF withdrawal, and decompressive craniotomy. Use of newer techniques of monitoring and treating cerebral edema should be reserved for centers experienced in the diagnosis and management of children with severe neurologic disorders. To date, groups employing these experimental measures have failed to demonstrate better survival rates than those providing intensive supportive care.

### What Therapies Are Directed At Removal of Presumed Toxins?

Exchange transfusion, dialysis, total body "washout," charcoal hemoperfusion, and plasmapheresis have all been suggested as potentially helpful by removing an unidentified toxic substance from patients with Reye's syndrome. There is no evidence that the use of these techniques improves outcome.

### What Are the Residual Findings?

Complete recovery may be expected in the majority of patients who survive the acute illness. However, some children who experience coma may suffer brain damage resulting in developmental delay, motor impairment, or mental retardation. Normal functioning in school may be delayed for some weeks. Children may be able to do the prescribed school work, but at a slower rate. Sometimes distractibility, inattention, and memory problems occur.

Anxiety and apprehension associated with fear of bodily harm and death are frequently encountered in these children while hospitalized and following discharge from the hospital. Such fears can be helped by gentle parental support. Overprotectiveness of the child by the parents can accentuate behavioral or school problems and should be avoided.

Extensive psychological and educational testing appears to be unnecessary except in a study setting. Assisting school personnel in providing learning experiences geared to the individual needs of the recovering child may be required. Family guidance and counseling may be useful and are encouraged.

### What Are the Areas of Future Research?

Potential areas of research include: epidemiology, etiology, pathogenesis, diagnosis, management, and outcome. Most important is elucidation of the etiology and pathogenesis of this syndrome, with prevention as the ultimate goal.

#### Epidemiology
The low incidence of this disease results in small numbers of patients available for study at any single institution. The designation of a specific diagnostic code for Reye's syndrome in the International Classification of Diseases (10th Revision, Clinical Modification) would facilitate the determination of a more accurate incidence rate for Reye's syndrome.

Studies stratifying cases by age, sex, and race, by socioeconomic and environmental characteristics, and by geographic areas and location of residence (urban, suburban, rural) are needed to elucidate factors which may be important.

**Etiology**

Although the etiology of Reye's syndrome remains unknown, an association with a recent viral infection, especially influenza B and varicella, is well established. However, the development of Reye's syndrome following any of these viral infections is uncommon, and why only certain individuals develop the disease deserves further study. In addition, three recent population-based case-control studies have demonstrated an apparent association between salicylate usage and Reye's syndrome. Since the specific questions posed to the panel and discussed at the consensus conference were limited to diagnosis and treatment, the data on which this association is based were not presented but were discussed by several participants in the conference. Each of the three studies indicates an increase in the estimated relative risk of Reye's syndrome, which does not appear to be due to chance. However, other possible explanations of this association include the following: potential biases such as case-control selection (e.g., comparability of antecedent illness), information gathering (e.g., based on recall), and confounding (e.g., indications for salicylate use).

Parents and physicians should be aware that most, if not all, medications have potential deleterious effects; thus, caution in the use of salicylates in children with influenza and those with varicella is prudent. Currently, the risk of these effects is unknown for salicylates or for other antipyretic medications. Since salicylates have been given to children with illnesses predisposing to Reye's syndrome without adverse effect, and cases of Reye's syndrome have occurred in which salicylates had not been administered, salicylates alone cannot be responsible for the development of Reye's syndrome. However, certain similarities between salicylism and Reye's syndrome and those studies reporting an association between Reye's syndrome and salicylate ingestion indicate a need for further carefully designed studies before recommending changes in antipyretic therapy of children.

The roles of influenza and other viruses, aflatoxins, and genetic predispositions also deserve study.

**Diagnosis**

Although guidelines for the recognition of Reye's syndrome are generally accepted, information on the validity of the many proposed screening (clinical and laboratory) tests is incomplete and based on small numbers of patients or nonuniform diagnostic criteria. Particular attention should be given to documenting the sensitivity, specificity, and predictive values associated with various tests.

**Management and Outcome**
Critical and comparative evaluation of the treatment of Reye's syndrome can only proceed within the framework of a randomized controlled trial. A need exists for determining the best available monitoring procedures, seeking the most sensitive indicators of patient status while exposing the patient to the minimal risk. Evaluations of treatment and monitoring regimens require strictly defined protocols and a sample size necessary for statistical analysis.

Both the short- and long-term sequelae related to Reye's syndrome should be evaluated. Subtle effects on mental and motor capabilities should be evaluated using longitudinal data analysis. When possible, evaluations should be conducted without knowledge of the patient's treatment or monitoring regimens.

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