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**Reye's Syndrome**

**S. M. MEHENDALE, K. BANERJEE**

**INTRODUCTION**

In April 1963, Anderson - described a few fatal cases of childhood encephalopathy in Australia, with post-mortem evidence of swollen brains and fatty liver. A few months later, Reye - encountered cases with similar pathological features but who also had raised blood transaminases, a reduced prothrombin time and diminished sugar levels in the serum and the cerebrospinal fluid (CSF). In the USA, Johnson - described similar cases during the influenza B outbreaks in October 1963. These three reports gave birth to a new clinical entity— "Reye's syndrome". 

Reye's syndrome (RS) is an acute, rare and serious multi-system disease which often follows a mild and unremarkable illness. Although it has been documented to be a major cause of neurological death in children in developed countries, its severity has remained unexplored in developing countries such as India.

**EPIDEMIOLOGY**

Reye's syndrome has a worldwide distribution. However, data on the incidence are poor and diagnosis depends very much on being aware of the disease and searching for it diligently. It has been described to be a rural and semi-urban disease, and hence, even in the absence of supporting data, would be expected to be a major problem in the Third World.

In India, cases were first reported in 1969 from almost all parts of the country except the Eastern region. It has been estimated that as many as 12 000 to 18 000 cases occur in India every year. Sporadic cases have been reported from Vellore, Chandigarh, Bangalore, Bombay and Delhi. However, it is possible that some cases are misdiagnosed to have acute encephalopathy or heat stroke.

Two distinct epidemiological patterns of RS have been described. It occurs in an epidemic form during or just

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National Institute of Virology, 20-A Dr Ambedkar Road, Post Box No. 11, Pune 411001, Maharashtra, India

S. M. MEHENDALE, K. BANERJEE

Correspondence to K. BANERJEE

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after influenza epidemics and as sporadic cases, probably in relation to chickenpox or other viral diseases. Therefore, although cases occur throughout the year, the greatest number of cases are seen from December to March, coinciding with peak influenza activity. In India, cases have been reported mainly during the summer and in the early monsoon months.

In the USA, a nationwide surveillance was initiated in 1973 by the Centers for Disease Control (CDC), Atlanta, Georgia and since 1976 there has been a continuous ongoing surveillance. Up to 1980, approximately 250 to 500 cases were reported annually. Since 1981, there has been a noticeable fall in the cases reported with 36 cases in 1987 and only 20 cases in 1988. However, it is possible that the estimate is faulty because reporting of cases is not compulsory, non-fatal cases are likely to be under-diagnosed and certain inborn errors of metabolism are erroneously included. In the UK, the surveillance was initiated in 1981. The annual incidence of RS in the USA is estimated to be 0.37 to 0.71 cases per 100,000 persons below 18 years of age. It is slightly higher in the UK and Australia (0.4 to 0.5), and this is 10 times higher than in other European countries such as Germany.

Reye's syndrome affects children of all ages with a peak between 5 and 15 years. However, since 1980 there has been a decline in cases among children between 5 and 10 years of age although the incidence among children below 5 years and children aged 10 to 19 years has been relatively stable. Instances of RS among neonates have been rarely reported and diagnosis in adults is based mostly on post-mortem examination.

The incidence of RS among females is marginally higher than in males. Whites are more prone than blacks except among infants in whom the relative risk in blacks as against whites is 8:1.

AETIOLOGY

The aetiology appears to be multifactorial and is not yet fully known. It is probably the result of virus-host interaction influenced by an exogenous agent in a susceptible individual with the end result being a metabolic derangement manifesting clinically as RS.

The following factors are thought to play a role in its causation.

Antecedent viral infections

Many viruses have been incriminated, the most common being influenza types A and B, and the varicella-zoster viruses. However, there is no direct evidence to prove that either viraemia or bacteraemia cause RS.

Clustering of cases of RS has been shown to be temporally and geographically related to influenza B outbreaks. In children below 18 years of age, one in every 2000 suffering from influenza B have been affected by RS. Similarly, there is a rise in the cases of RS during varicella epidemics in which its incidence is believed to be 1 in 4000. In the USA, 5% to 30% of cases have been shown to be associated with antecedent varicella and 43% cases followed influenza attacks.

A vast range of viruses—adenoviruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), mumps, Coxsackie A and B, dengue, herpes simplex, respiratory syncytial virus, parainfluenza, rubella, polio and echoviruses have been reported to be associated with RS. Dual viral infections are also thought to be important in its causation.

Exogenous medication

Four case-control studies conducted between 1980 and 1982 in the USA demonstrated an association between RS and aspirin consumption during an antecedent illness. Simultaneous studies in the UK also led the 'Committee on Safety of Medicines' to corroborate the fact that such an association existed. However, most of these studies were retrospective and serious objections have been raised about the validity of their conclusions in view of their information, selection and confounding biases. Subsequently a task force was set up which planned and executed a pilot study and then the main study, after careful elimination of errors in the earlier study design. The association between RS and aspirin was established; but its causality was not confirmed.

Salicylates (mainly aspirin), acetaminophen and anti-emetics have been incriminated in the causation of RS. Lovejoy reported a higher mortality in cases of RS who had consumed higher aspirin doses. Similar conclusions were reached by Starco and in Ohio and Michigan.

Although the first conclusive evidence of the RS-aspirin association was provided in 1980, definite action was taken by the Food and Drugs Administration (FDA) in the USA only in 1986. It advised that the drug should carry a 'package label warning'. Earlier, in 1980, the US Surgeon General had merely advised doctors and parents against the use of aspirin in viral fevers, especially influenza and chickenpox.

Only a population-based prospective study can define the risk of RS attributable to salicylate use; however, aspirin should preferably be avoided in the treatment of viral fevers.

Genetic predisposition

Many instances occurred in which families had more than one member who had RS. Some reports suggested that metabolic differences existed between the members of such families compared with others. Certain inborn errors of metabolism such as disorders of ureagenesis, branched chain amino acid metabolism and ketogenesis also have clinical and laboratory abnormalities similar to those of RS. Hence it was hypothesized that some children may be genetically predisposed to the condition. However, it is probable that environmental factors and exposure to infection play a major role. During metabolic stress, a genetic enzymatic defect in ammonia metabolism may be expressed as RS. No cases have occurred among identical twins and only some siblings suffering from the same prodromal illness develop RS. These observations do not support the role of genetic factors in the causation of RS. Therefore, more elaborate studies in familial genealogy, matched twins, siblings and adopted children may provide evidence in this regard.
Environmental factors
Due to the absence of strong evidence in favour of a genetic aetiology and a less than clear-cut correlation between RS and antecedent viral infections, it has also been hypothesized that exposure to environmental toxins leads to RS.

The clinical presentation and liver histology in aflatoxin poisoning are similar to RS and this has been reported in studies from Thailand and Czechoslovakia. Aflatoxins also cause a RS-like illness in monkeys.

In North-Eastern Canada and Thailand, RS cases have been reported from areas covered under forest insecticide spraying operations as well as in association with the use of certain chemicals in agriculture. However, in spite of animal and in vitro evidence, a definite link between RS and toxins, insecticides and chemicals has not yet been established.

PATHOGENESIS
Although viraemia or bacteraemia have not been demonstrated in cases of RS, the disease has a clinical picture similar to that of a toxemia. It appears to be a metabolic response to a generalized multi-system mitochondrial insult, but, the exact pathophysiological sequence linking the various suspected aetiological agents to mitochondrial injury remain unexplained.

Well characterized pathological features of RS are:

Reversible injury to mitochondrial structure and function
Mitochondria are affected in the liver, brain and other organs. Mitochondrial alterations seen under the electron microscope (EM) include expansion and disorganization of the matrix, pleomorphism, progressive loss of matrix-dense bodies and gross swelling which may lead to rupture of the outer membrane. However, regardless of cerebral outcome, mitochondria become normal after a certain period of time.

Cerebral oedema
Primary cerebral insult is possibly a result of insufficient substrate availability which causes massive cytotoxic cerebral oedema.

Intensive catabolic phase
A very severe phase of systemic catabolism of fats, proteins and carbohydrates results in most of the metabolic consequences of RS which are summarized below.

Hyperammonaemia. It results subsequent to the severe catabolic state. Due to a loss of the hepatic enzymes—carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC)—the liver cannot effectively detoxicate ammonia into urea. The concentration of ammonia in the arteries and jugular veins increases, leading to an acute uptake of ammonia by the brain; and vomiting, confusion, ataxia and hyperventilation follow. The severity and mortality of RS is often related to the degree of hyperammonaemia.

Fatty and organic acididaemia. Excessive free fatty acids (FFA) are released due to excessive lipolysis. In the impaired liver, microvesicular droplets of triglycerides produce fatty infiltration. The illness in patients with initially higher FFA levels is usually more severe than in those in whom these are lower.

Hyperlactataemia and lactic acidosis. Excessive production of lactic acids in the brain and muscles, ineffective utilization of lactate by the liver and kidneys and hyperventilation result in a sluggish hepatic flow in patients with RS and this has been observed to be directly related to the level of hyperlactataemia.

Thus, RS is a disease entity which manifests chemically as hepatopathy and clinically as encephalopathy.

CLINICAL FEATURES
Assuming antecedent viral illness to be the main aetiology, many researchers have described two phases of the illness—the infective phase and the encephalopathic phase or classical RS.

Symptoms
Intractable vomiting is often the symptom reported first. Due to brain dysfunction, the child may have disorientation, lethargy and personality changes like unprovoked shouting and use of abusive language. Finally the patient becomes comatose. There is no fever, jaundice, loss of memory, sleep disturbance or intellectual retardation. Infants may present with respiratory distress (apnoeic spells), seizures or hepatomegaly.

Signs
The affected child is often disoriented and neurological signs commonly elicitable are coma, dilated pupils, decerebrate or decorticate posture and, very rarely, involuntary movements. Hepatomegaly may be seen in 30% to 40% of cases. Signs of meningeal irritation and localizing neurological signs are usually absent.

Staging of RS
In the report of the Consensus Conference on the Diagnosis and Treatment of Reye's syndrome, five stages were described (Table 1).

The neurological state may stabilize or improve at any stage short of brain death and the child may recover completely. The cause of death in RS may be swelling of brain cells causing cerebral and cerebellar herniation, increased intracranial tension and brain hypoxia or medullary coning and pressure on the vital brain centres. Post-mortem may show an enlarged and pale grey liver and diffuse swelling of the brain. Cerebral or cerebellar herniation, petechial haemorrhage in the intestine and swollen and pale kidneys are the other findings.

LABORATORY INVESTIGATIONS
The diagnosis of RS is mainly clinical, but a few laboratory tests may help in diagnosing cases at an early stage facilitating prompt hospitalization and case management and thus reducing mortality.

Serum transaminases
The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values are found to be raised in
Table I. Clinical staging of Reye's syndrome

<table>
<thead>
<tr>
<th>Sign</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Lethargic but</td>
<td>Combative or</td>
<td>Coma</td>
<td>Coma</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>follows verbal</td>
<td>stuporose,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>commands</td>
<td>inappropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>Normal</td>
<td>Decorticate</td>
<td>Decerebrate</td>
<td>None</td>
</tr>
<tr>
<td>Response to pain</td>
<td>Purposeful</td>
<td>Purposeful/</td>
<td>Decorticate</td>
<td>Decerebrate</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>non-purposeful</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupillary reaction</td>
<td>Brisk</td>
<td>Sluggish</td>
<td>Sluggish</td>
<td>Sluggish</td>
<td>None</td>
</tr>
<tr>
<td>Oculocephalic</td>
<td>Normal</td>
<td>Conjugate deviation</td>
<td>Conjugate deviation</td>
<td>Inconsistent/absent</td>
<td>None</td>
</tr>
</tbody>
</table>

almost every case. The rise in ALT was considered to be an important diagnostic criterion if it was more than three times the normal level. However, recent studies have shown that this rise may be only transitory and not large.

**Blood ammonia**

Many researchers have observed blood ammonia levels to be raised to more than three times the normal levels in RS. Considered alone, the diagnostic utility of this test is limited, but if it is considered together with the degree of coma and raised prothrombin time, then the precision of diagnosis is increased.

**Prothrombin time**

The prothrombin time is prolonged in more than 80% of cases.

**Liver biopsy**

The liver biopsy and histopathology are of great diagnostic value even in cases of stage I RS. The light microscopic criteria for RS are panlobular accumulation of lipid droplets and absence of zonal necrosis, cholestasis and lobular inflammation (Fig. 1). The electron microscopic (EM) changes are mitochondrial expansion, proliferation of smooth endothelial reticulum, glycogen depletion, peroxisomal proliferation, irregularity of mitochondrial membranes and reduction in matrix granules (Fig. 2).

Bannet, however, feels that as fatty change in the liver is common it should not be considered important in diagnosis. Liver biopsy increases the certainty of the diagnosis in infants, children with recurrent episodes, patients with a history of similar attacks in the family and suspected cases of RS who do not have any antecedent illness or vomiting. However, care must be taken in the case of critically ill children with coagulation defects to avoid the complications associated with the procedure. A judiciously performed biopsy of the liver can help in early detection of RS and also may help to predict whether the pathological process is reversible.

**Cerebrospinal fluid examination**

Examination of the CSF in cases of RS reveals 8 or less cells per cmm and normal levels of protein and sugar. Low levels of sugar in CSF have also been reported. The lumbar puncture may in some cases lead to neurological deterioration and should be avoided if coma is progressing rapidly.

**Assays for mitochondrial hepatic enzymes**

There is an overall decrease in the levels of certain mitochondrial enzymes such as ornithine transcarbamylase pyruvate dehydrogenase, glutamate dehydrogenase and succinate dehydrogenase. These changes may remain many hours after death. Indeed some feel that RS should not be accepted as a diagnosis if the enzyme levels are not altered.

**Blood biochemistry**

**Blood glucose.** Hypoglycaemia is common in severely ill children below 2 years of age. In other age groups it is present in only 15% to 18% cases.

**Serum bilirubin** is normal and may rarely be raised.

**Serum FFA.** During the acute phase of RS, the medium and long chain FFA levels are raised.

**CAT scan**

There is no indication for CAT scan in RS unless a subdural haematoma or a brain abscess is suspected. In the early stages of RS, the CAT scan may show diffuse brain oedema without any displacement of the ventricles or localized areas of enlargement.

**DIAGNOSIS**

RS was not even considered in the differential diagnosis of acute encephalopathy till 1980 when the Centres for Disease Control, USA laid down the diagnostic criteria. Epidemiological case definition describes RS as

An acute non-inflammatory encephalopathy often marked by persistent vomiting, altered sensorium or coma with (i) biopsy or autopsy confirmed fatty liver or (ii) serum ALT or AST or ammonia level three times more than the normal and CSF showing 8 or less leucocytes per cmm and no other reasonable explanation for hepatic or neurological abnormalities.

However, most authorities take an 'acceptable definition of RS' as a compatible clinical illness with the histological finding of microvesicular fatty infiltration of the liver. In the absence of histological evidence of fatty liver, RS is certainly a possibility if encephalopathy is accompanied...
Differential Diagnosis

The differential diagnosis of RS in infants is different from that in other age groups. In infants it should be distinguished from the inborn errors of metabolism and the near-miss Sudden Infant Death Syndrome (SIDS). In other age groups patients with similar clinical features, i.e. vomiting, coma or raised transaminases may have, hypoxia, lead or aflatoxin poisoning, endotoxaemia, hypoglycaemia and reactions to aspirin or valproate.

To diagnose a case of RS in a child below 3 years of age, metabolic and genetic disorders which closely mimic the disease should be excluded. These are:

(i) Disorders of ureagenesis, e.g. partial ornithine transcarbamylase deficiency.
(ii) Disorders of branched chain aminoacid catabolism, e.g. propionyl co-A carboxylase deficiency.
(iii) Disorders of ketogenesis, e.g. systemic carnitine deficiency and Acyl co-A dehydrogenase deficiency.

Though sophisticated tests are available to diagnose these metabolic disorders, in developing countries like India, these are not available. Therefore genetic metabolic disorders may be missed and such patients may be diagnosed erroneously to have RS.

Management

Patients with RS need admission to hospital, preferably in paediatric intensive care units. Management should be aimed at correction of metabolic disturbances and reducing the cerebral oedema. The treatment of RS is empirical because there is no specific treatment for the mitochondrial insult.

Hospitalization and intensive care management instituted at an early stage of the illness reduces the mortality but this is often not possible unless medical practitioners have a high index of suspicion.

Treatment of metabolic abnormalities

The child should be immediately given intravenously 1500 to 1800 ml of 5% or 10% dextrose per square metre of body surface area per day. Vitamin K administration has also been found to be useful. Transfusion may be necessary if there has been major blood loss.

Monitoring and control of intracranial pressure

The intracranial pressure should be monitored in patients with RS, but should only be done in well-equipped hospitals to minimize the mortality associated with the procedure. The pressures in the epidural, subarachnoid and ventricular spaces are recorded.

Control of intracranial tension (ICT) is the primary objective of treatment. This may be done by endotracheal catheterization and spontaneous or controlled hyperventilation and intravenous mannitol. High doses of barbiturates and corticosteroids have not been shown to be of much benefit. Invasive measures such as CSF tapping and extreme measures like decompression craniectomy have a questionable utility.

Well equipped hospitals may follow the successful 'Glasgow regimen' in the management of RS, as outlined by the Children's Hospital, Washington.

1. Put a catheter in the child's skull and continuously monitor the ICT.
2. Start intravenous fluids.
3. Put a nasogastric tube for feeding and give antacids to prevent ulceration of the gastrointestinal tract. Place a catheter in the bladder.
4. Movements by the child may increase ICT, therefore, immobilize the patient and put him or her on a respirator. Use hyperventilation to reduce the ICT.
5. Osmotherapy: Clinical signs resulting from increased ICT in RS are related to the development of cerebral oedema. Hence for reducing ICT, give intravenous mannitol and if this fails give glycerol. If ICT does not fall, coma should be induced by giving pentobarbitone and morphine along with dexamethasone for this purpose. However, if these are used the child may take many days to recover from coma.

If everything else fails, decompression craniectomy may be performed by removing two flaps from the skull bones of the child. After this procedure some children have recovered without any neurological deficit. In addition, presuming that certain toxins cause RS, measures to eliminate them such as exchange transfusion dialysis, total body washout, charcoal haemoperfusion and plasmapheresis have been tried. However, the results have been unsatisfactory.

Prognosis

The early picture of 90% mortality and 10% recovery in 1963 has radically changed and the mortality in developed countries has dropped to between 20% and 30%. However, the mortality reported in India is still very high, i.e. 80% to 90%. This is possibly because cases have been detected only in the late stages of the disease.

With early diagnosis and prompt hospitalization the prognosis is better. High serum ammonia and FFA levels indicate a bad prognosis and a fall in these is soon followed by clinical recovery. Patients with a rapid clinical course leading to coma have very little chance of survival. As many as 16% to 36% of surviving children suffer permanent brain damage manifesting as neuropsychological problems, developmental delay or motor impairment. However, it has been observed that in spite of a clinically severe attack and deep coma, complete functional recovery is possible.

Conclusions

It is important to discover the aetiology of RS to develop a rational policy for its prevention. A surveillance system should be designed to monitor its incidence, seasonality, demographic features and possible association with viral outbreaks. A specific diagnostic code may help in estimating this incidence more accurately and a sensitive
screening test may be devised to enable medical practitioners to diagnose cases of RS in its early stages. Animal models should be developed which may prove to be useful in studying aetiology, discovering and perfecting new investigative methods and testing the virulence and encephalopathic potential of different virus strains.

Dissemination of information with respect to early symptoms, diagnostic criteria and essential aspects of therapy through education of parents, physicians and nurses may increase the awareness regarding the condition. Salicylates should be avoided during chickenpox or influenza epidemics. However, only after the exact aetiology of RS is discovered will we succeed in preventing and ultimately controlling this serious disease.

REFERENCES