Reye's Syndrome

Description[1]

This is a rare syndrome, characterised by an acute, life-threatening, non-inflammatory encephalopathy and fatty degeneration of the liver with minimal or no clinical signs of liver involvement. In classic Reye's syndrome, there is a severe but self-limiting disturbance of mitochondrial structure and associated enzymatic disturbances usually lasting about six days. This is accompanied by an intense, acute catabolic state associated with cerebral oedema in the absence of encephalitis or meningitis.

The pathogenesis of Reye's syndrome is unclear but it appears to involve mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty-acid beta-oxidation in a virus-infected, sensitised host. The host has usually been exposed to mitochondrial toxins, most commonly salicylates (>80% of cases). Histologically the mitochondria are seen to become swollen and reduced in number. The liver and kidney are both affected. Changes in the brain result in cerebral oedema and increased intracranial pressure (ICP).

This condition appears to be a very rare complication of common viral infections. It often occurs after an unremarkable viral infection, particularly following influenza B, influenza A, varicella or parvovirus infections.[2] It has also been reported after gastroenteritis and even live-virus vaccines. Measles has not been implicated. It is thought to come about as a result of interactions between viral and toxic environmental factors, with the most likely mechanism being an interaction of toxic substances on mitochondria that have been sensitised by the viral infection.

The most intensively investigated toxic factor has been salicylate (usually in the form of aspirin).[3] This has been because of epidemiological associations (aspirin is involved in >80% of cases, although this has not been geographically universal) and because of histopathological similarities between liver changes in Reye's syndrome and in those found in acute salicylate poisoning.

Other drugs that have been used in patients who have developed Reye's syndrome have included outdated tetracycline, valproic acid, zidovudine, didanosine and anti-emetics. Reye's syndrome or Reye-like syndromes have also been associated with insecticides, herbicides, aflatoxins, paint, paint thinner, margosa oil, hepatotoxic mushrooms, hypoglycin in ackee fruit (Jamaican vomiting sickness) and herbal medications with atractyloside (a diterpenoid glycoside found in the extracts of the tuber of Callilepis laureola - impila poisoning).

Reye-like illnesses have also been described whereby there is a similar pathological picture but associated with inherited metabolic disorders such as urea cycle defects, alpha-1 antitrypsin deficiency, fructosaemia, etc.[4] Fatty-acid metabolism disorders seem to be more implicated. The number of these disorders reported to present with a Reye-like syndrome is increasing. Cystic fibrosis is one of these conditions. The current belief is that Reye's syndrome is very rare and any child presenting with it should be tested for inborn errors of metabolism.[5] It is certainly true that, since the ban on the use of aspirin under the age of 12 in 1986, it has declined and it is argued that better diagnosis of metabolic abnormalities will not account for all this. It is possible that other factors as yet unknown are implicated - change in the genetic code of a virus has been mooted.[1] In 2002 the ban on aspirin was raised to 16 years old.[6]

In 2008 a report was published in the British Medical Journal implicating the use of salicylate-containing oral gel in a patient with suspected Reye's syndrome. Although the case was eventually diagnosed as salicylate toxicity, the fact that a significant level of the drug was found in the patient's bloodstream led to the Health Protection Agency issuing a warning on the use of salicylate oral gels in the under-16s. The products affected were Bonjela® and Bonjela Cool Mint®. A warning was also issued about Pyralvex®, a paint used for dental pain/oral ulcers.[7]
Epidemiology

Reye's syndrome is a rare disease. There has been a significant decrease in the classic Reye's syndrome cases as a result of the restriction of salicylates in children.\(^4\) Seasonal variation was between December and April when flu-like illnesses were most prevalent but, in recent years, the sporadic cases to not exhibit such a pronounced seasonal effect.

An association has been shown to exist between Reye's syndrome and the use of aspirin during the prodromal illness. The falling incidence is lauded as a public health success, informing the public about the dangers of giving aspirin to children under 12.\(^3\) However, Reye's syndrome can occur in older children and even in adults. Teenagers should also be advised to use ibuprofen and paracetamol rather than aspirin.

The usual presentation is between 5 and 14 years with a median of 7. It is rare over 18 but can occur in the first year of life.

Presentation

- This syndrome usually occurs in a child with an unremarkable medical history, 3-5 days after the recovery phase of an unexceptional viral illness.\(^1\) Most frequently, this is an upper respiratory tract infection, influenza, varicella, or gastroenteritis. Other viral illnesses may be associated.
- The typical patient abruptly deteriorates, typically about three days after apparent improvement. Initially there is protracted vomiting (rarely, this may be absent), followed by listlessness, lethargy and drowsiness 24 hours to 48 hours later. This is associated with tachypnoea.

> Use of anti-emetics has been linked to the aetiology and may complicate the presentation by masking the vomiting aspect of the presentation.

- The first sign in younger patients (under the age of 2) may simply be diarrhoea and tachypnoea.
- The patient may continue to deteriorate, with more prominent neurological symptoms. Initially this may be a withdrawn state. It is followed by delirium and confusion, combative behaviour and stupor. There may be visual hallucinations.
- There may be sluggish pupillary responses but ophthalmological features of raised ICP are not always present.
- The clinical deterioration can continue, sometimes progressing to seizures and coma. Decerebrate posturing, opisthotonos, dilated/unequal pupils, deep rapid respirations, variations in pulse and, finally, a flaccid apnoeic state precede death.

Liver function is impaired, sometimes with slight hepatomegaly but without jaundice. The course of the illness may vary (4-60 hours) and the neurological status may stabilise or improve (spontaneously or with therapy) at any stage short of brain death.

In infants, the presentation is with more predominant respiratory symptoms and signs (tachypnoea, respiratory distress, hyperinflation and apnoea) ± temperature instability. Hypoglycaemia and hepatomegaly are more common and vomiting is usually absent. The history of a preceding viral infection is less common.

Investigations\(^8\)

Biochemistry

- Biochemical evidence of liver dysfunction is always found. Transaminases are markedly elevated. Elevated bilirubin is less common.
- The prothrombin time is usually very slightly prolonged. Check INR.
- Ammonia levels may be up to 1.5 times the normal level.
- Hypoglycaemia must be identified and treated - it is a feature of severe cases, particularly in children under the age of 2.
- Measurements should also be made of U&Es, bicarbonate, magnesium, calcium and phosphate levels. Serum osmolality should be checked as should blood ammonia and creatinine phosphokinase levels.
- Salicylate levels should be checked.
- There are a number of metabolic events that occur secondary to Reye's syndrome and these may be reflected in the blood biochemistry - eg, very high levels of growth hormones, glucagon, fatty acids and glycerol. Lipase and amylase levels will also be elevated.
- Lactate dehydrogenase may be high or low.
- Urine specific gravity is raised and 80% of patients have ketonuria.

**Other investigations**
- Check FBC and arterial blood gases.
- CT or MRI of the head may reveal cerebral oedema but often it is normal.
- Lumbar puncture (LP) - if ICP is not elevated - may be required to exclude other causes such as meningitis but is contra-indicated in typical cases:
  - If LP is required, the patient needs to be ventilated and a CT scan should be done first to rule out intracranial ventricular compression. The patient should be haemodynamically stable prior to LP.
  - Opening pressure may be normal or increased.
  - CSF is usually normal apart from a low sugar concentration.
- Liver biopsy (if performed) shows swollen, pleomorphic mitochondria, poor gluconeogenesis and ureagenesis. Coagulation defects must be corrected before biopsy.
- EEG may be helpful - it shows slow waves in the early stages and flattened waves later on.

As the patient stabilises following the acute phase, inherited disorders of metabolisms should be actively sought and ruled out.

**Diagnosis**
The diagnosis is one of exclusion as there are no specific tests. However, diagnostic criteria for Reye's syndrome have been proposed:

- Acute non-inflammatory encephalopathy with an altered level of consciousness.
- Hepatic dysfunction with a liver biopsy showing fatty metamorphosis or a more than three-fold increase in ALT, AST and/or ammonia levels.
- No other explanation for cerebral oedema or hepatic abnormality.
- CSF with a maximum of $8 \times 10^9/L$ white blood cells.
- Brain biopsy: cerebral oedema without inflammation.

**Differential diagnosis**
A child presenting with Reye's syndrome has to be assumed to have an *inborn error of metabolism* (particularly if under the age of 4) until proven otherwise. Other differentials to consider when presented with these cases include:

- Meningitis.
- Encephalitis.
- Hepatitis.
- Salicylate poisoning.
- Other toxic ingestion, poisoning or drug overdose.
- Diabetes (there may be ketonuria in Reye's syndrome due to vomiting).
- Hypoglycaemia.
- Head injury.
- Acute kidney injury or hepatic failure.
- Intussusception.
- Paediatric sepsis.
- Paediatric gastroenteritis.
- Sudden infant death syndrome.
Staging of Reye's syndrome

The original staging was 1 to 5 but now it is 0 to 6. Staging is valuable to aid management and for retrospective assessment of prognosis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>0.</td>
<td>No clinical abnormality but there are biochemical abnormalities suggestive of the disease.</td>
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<tr>
<td>1.</td>
<td>Lethargic, sleepy and vomiting. Investigations indicate liver dysfunction.</td>
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<td>3.</td>
<td>Unrousable, predominantly flexor motor responses (decorticate).</td>
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<tr>
<td>4.</td>
<td>Unrousable, predominantly extensor responses, fixed dilated pupils (decerebrate).</td>
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<tr>
<td>5.</td>
<td>Unrousable, flaccid paralysis, seizures, absent tendon reflexes, unresponsive pupils, respiratory arrest.</td>
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<tr>
<td>6.</td>
<td>Cannot be classified because of treatment with curare or other medication that alters levels of consciousness.</td>
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Management

Successful management of the disease depends on early diagnosis. It is aimed at preventing, correcting and minimising metabolic abnormalities and controlling increased ICP. Early recognition and treatment are essential to prevent death and lifelong neurological impairments.

Important aspects of management are outlined here but not appropriate (or possible) in primary care. The remit of the general practitioner is to recognise the condition early and refer urgently.

- It is worth noting that the patient should be kept as quiet as possible; unnecessary handling or stimulation raises the ICP.
- Establish and maintain the patient's airway, breathing and circulation as needed.
- Check the glucose level, particularly if the patient is younger than 1 year, has an altered mental status or both. Administer dextrose to manage hypoglycaemia.

There is no specific treatment for Reye's syndrome. Treatment is supportive. On admission, some of the steps taken in initial management will include:

- Maintaining airway and brain oxygenation.
- Immediately correcting any hypoglycaemia with IV glucose and setting up a 10% glucose infusion. Blood sugar levels should be between 11 mmol/L and 22 mmol/L (ie higher than normal).
- If the blood pressure is normal, the head and upper trunk should be elevated at a 40° angle and overhydration avoided.
- Monitoring and controlling blood chemistry and avoiding dehydration.
- Ondansetron may be cautiously used to control the vomiting. Antacids may also be prescribed.
- Hyperammonaemia may be treated with sodium phenylacetate/sodium benzoate or haemodialysis.
- Controlling fever.
- Anticonvulsants (eg, phenytoin) may be required to treat seizures (if they are used in the acute phase, they are likely to be required for a number of months after recovery).
- Correction of coagulation defects if PTT exceeds 16 seconds; vitamin K may be needed to correct bleeding.
- Expert colleagues should be consulted early and admission to paediatric ITU sought.

Stage 2 or worse needs referral to a tertiary centre where ICP can be monitored and lowered with appropriate therapy. Other parameters (central venous pressure, blood biochemistry abnormalities, coagulopathies, seizures, etc) will also need to be carefully managed.

A case of fulminant hepatitis successfully treated with liver transplantation has been reported.[9]

Complications

- Brain herniation with its complications.
- Acute respiratory failure.
- Cardiovascular collapse.
- Aspiration pneumonia.
- Gastrointestinal bleeding.
- Pancreatitis.
Prognosis

Prognosis has improved greatly with improvements in early diagnosis, recognition of milder cases and aggressive treatment. If cerebral oedema is controlled, there is complete recovery. Between 65% and 75% of patients admitted during stages 1 or 2 make a full recovery.

The overall mortality rate is currently around 20%. 10% to 20% have a persistent neurological deficit with a range from slight to profound. Ammonia level is the best predictor, with approximately 3% of patients experiencing neurological sequelae if levels are less than 45 μg/dL and 11%, if more than 45 μg/dL. Prognosis is worse in younger children (<5) and in more advanced illness, death rates rising to 85% in stage 5. Other factors suggesting a poor prognosis include:

- Rapid progression of symptoms to grade 4 encephalopathy.
- Creatinine phosphokinase >10 times normal.
- AST:ALT ratio less than 1.
- Marked slowing on electroencephalogram (EEG).
- High non-esterified fats.
- High long-chain dicarboxylic acids.
- Hypoprothrominaemia unresponsive to fresh frozen vitamin K and fresh frozen plasmas.

Prevention

There appears to be good evidence that the avoidance of aspirin in children with febrile illness has had a dramatic effect on the incidence of Reye’s disease, although the evidence of the association is not conclusive. It is important to avoid aspirin where possible and, where alternatives exist, probably until the age of 16 or even 18. Kawasaki disease is usually treated with high-dose aspirin and Reye’s syndrome following this has been reported but is very rare indeed (1 in 200,000 children with Kawasaki disease in one Japanese study). The risks and benefits of influenza and varicella vaccines should be weighed up in children taking salicylates on a long-term basis.

Further reading & references

- Reye’s Syndrome; National Institute of Neurological Disorders and Stroke
- National Reye’s Syndrome Foundation UK

6. Aspirin and Reye’s Syndrome; Medicines and Healthcare products Regulatory Agency, 2005 (archived content)
7. New advice on oral salicylate gels in under 16s; Medicines and Healthcare products Regulatory Agency, 2009 (archived content)

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