Reye's Syndrome in Children

Supriatmo
Departemen Ilmu Kesehatan Anak
Fakultas Kedokteran Universitas Sumatera Utara

Abstract: *Reye's syndrome (RS) is a rare but potentially fatal disease that affects all organ of the body, with an especially devastating attack upon the liver and brain. It is characterized by encephalopathy with severe edema of the brain, increased intracranial pressure, hypoglycemia, and the fatty infiltration of the liver. Prognosis according to the duration of disordered cerebral function during the acute stage of illness is the best predictor of eventual outcome. In patients with grade I disease, recovery is rapid and complete. The cause of Reye's syndrome is not clear. Epidemiology methods have established a statistical association between aspirin ingestion during an antecedent viral infection and Reye's syndrome, but they cannot establish causality non can they expose the biologic mechanism of the disease.*
Keyword*: reye's syndrome, encephalopathy, aspirin, viral infection*

Abstrak: *Sindroma Reye merupakan penyakit yang jarang dijumpai tetapi berakibat sangat fatal, ditandai dengan adanya ensefalopati dan menyerang hamper semua organ. Tidak ada alat bantu diagnostik yang khusus untuk menegakkan sindroma Reye ini. Biopsi hati mempunyai arti penting pada sindroma Reye. Penyebab sampai saat ini masih belum jelas. Aspirin dihubungkan dengan kejadian sindroma Reye. Prognosis berhubungan dengan stadium penyakit saat pertama dikenali. Dilaporkan satu kasus sindroma Reye pada seorang anak laki-laki usia 2 tahun 2 bulan, pada awal masuk pasien didiagnosa dengan ensefalitis. Tidak diketahui penyebab sindroma Reye pada kausus ini.*

INTRODUCTION

Reye's syndrome (RS) is a rare but potentially fatal disease that affects all organ of the body, with an especially devastating attack upon the liver and brain. It is characterized by encephalopathy with severe edema of the brain, increased intracranial pressure, hypoglycemia, and the fatty infiltration of the liver. It is two phase of illness, almost always associated with a previous viral infection. In the US, the frequency, which peak in the 1970s and early 1980s, is now < 0.03-1 case per 100.000 persons younger than 18 years, though it may be as high 6 cases per 100.000 with a regional epidemics.

The racial distribution of RS in the United States, according to CDC surveillance statistics in 1980-1997 is 93% white; 5% African American; and the remainder Asian, American Indian, and Native Alaskan. RS is equally distributed between the sexes, the peak age are 5-14 years, with a median of 6 years and a mean of 7 years.

Although the etiology of RS is unknown, the condition typically occur after a viral illness, particularly an upper respiratory tract infection, influenza, varicella, or gastroenteritis, and it is associated with the use of aspirin during the illness. The discovery of inborn errors of metabolism that have manifestation similar to those of RS and a dramatic decrease in the use of aspirin among children have made the diagnosis and occurrence of RS rare.

The pathogenesis is unclear, but it appears to involve mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty acid beta oxidation in a virus infected, sensitized host. The host has usually been exposed to mitochondrial toxin, most commonly salicylates. Some have postulated that salicylate stimulate the expression of inducible nitric oxide synthase (iNOS) because of findings of iNOS stimulation in African children with fatal malaria. Malaria causes symptoms similar to those RS and is often treated with aspirin.

Table 1. Clinical staging of Reye's Syndrome

Grade	Symptoms
I	Usually quiet, lethargic and sleepy, vomiting, laboratory evidence of liver dysfunction
II	Deep lethargy, confusion, delirium, combative, hyperventilation, hyperreflexic
III	Obtunded, light coma, seizure, decorticate rigidity, intact papillary light reaction.
IV	Seizures, deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, fixed pupil.
V	Coma, loss of tendon reflexes, respiratory arrest, fixed dilated pupils, flaccidity.decerebrate (intermittent); isoelectric electroencephalogram

Hystologic changes include cytoplasmic fatty vacuolization in hepatocytes, astrocyte edema, loss of neurons in the brain, edema and fatty degeneration of proximal lobules in the kidney. All cells have pleomorphic, swollen mitochondria that are in reduced number, along with glycogen depletion and minimal tissue inflammation. Hepatic mitochondrial results in hyperammonemia, which is thought to induce astrocyte edema, resulting in cerebral edema and decrease intra cranial pressure.

Given that manifestations of RS are unique to RS but also seen in other conditions, are given that no test is specific for RS, the diagnosis must be one of exclusion. A high index of suspicion is critical for diagnosis. With the recognition that RS is rare, the diagnosis should be considered in any child with vomiting and altered mental status.

Since patients with Reye's syndrome may progress to deeper levels of coma over the first 24 to 72 hours of the illness, once initial stabilization of the patients has been achieve, referral to a pediatric centre with intensive care capabilities is mandatory. Initial stabilization for most patients involved blood volume expansion with crystalloid to correct hypotension or dehydration, restoration of blood glucose levels, oxygen, antiseizure medications, or sedation with short-acting barbiturate. Prior to transfer, osmotherapy (mannitol) and endotracheal intubation with assisted ventilation may be needed in those severe case already in coma or showing rapid progression to deeper levels of coma.

Prognosis according to the duration of disordered cerebral function during the acute stage of illness is the best predictor of eventual outcome. In patients with grade I disease, recovery is rapid and complete. In patients with more severe disease there may be subsequent subtle neuropsychologic defects noted (in intelligence, school achievement, visuomotor integration, and concept formation).

CASE

A-two year and two month old boy was admitted to Pediatric Intensive Care Unit H.Adam Malik Hospital with main complain was decreasing of consciousness since 6 hours before admitted. Followed by generalized seizure about 5 minute. He got feverish since 3 days, vomiting and diarrhea for 3 days. He already hospitalized in a private hospital but whenever no improvement the parents brought the patients to H.Adam Malik Hospital. From the physical examination showed an-unconsciousness (GCS 6) boy, BW 11 kg, temperature 38.8 ^{o}C. There was nuchal rigidity. Heart rate 140 time per minute, no murmur. Respiratory rate 30 times per minute without rales. Enlargement of the liver 2 cm below right arch rib. Differential diagnosis was encephalitis and meningoencephalitis with unstable cardiovascular system. Treatment with antibiotic ceftriaxon and ampicillin intravena, dexamethason and dilantin to control seizure. Zovirax iv drip in NaCl 0.9%. Lumbal puncture suggested to encephalitis. Laboratory finding; Hb 11.4 g/dl, leukocyte 12.800/mm^3, thrombocyte 130.000/mm^3, Blood gluce 67 mg/dl, electrolytes were normal, SGOT 362 u/L, SGPT 362 u/L. Phosphatase alkaline 154 u/L, ureum 54 mg/dl, creatine 0.3 mg/dl, uric acid 12.2 mg/dl. Diagnosis was encephalitis and Hepatitis. Treatment was continued, add urdafalk 10 mg/kg in 3 doses. Repeat blood glucose, liver biochemical, electrolyte, Blood gas analysis. Laboratory findings resulted; recurrent hypoglycemia, with mild acidosis and showed hyperactivity of liver while SGPT 1120 u/l, SGOT 1245 u/L. Liver enlargement 10 cm below right arch rib and spleen were palpable in Schuffner II. The treatment continued with glucose 40% bolus to control hypoglycemia. Mannitol and stabilized all the organ system. The next day, patient has GI bleeding, and decreasing of consciousness and deeper coma. The patient was fasting and give total parenteral nutrition including carbohydrate, protein and fatty acid. Liver enlargement continued uncontrolled with increasing level of SGPT and SGOT two fold than the previous day. We inserted the central vein catheter, the patients showed progressive destructive of the liver and hematologic system was suppressed with lower Hb and thrombocyte. The GI bleeding remain uncontrolled. Some time the seizure occurred and the coma was going worst and deeper. We made Reye's syndrome as diagnosis although there was history of aspirin ingestion and previous viral illness. All the physical examination, laboratory finding pretend to Reye's syndrome. We planned to perform liver biopsy but unfortunately we loss him before have the results.

DISCUSSION

The diagnosis of Reye's syndrome in this case was established based clinical presentation and supported by laboratory examination. In admission, the sign and symptoms presenting like encephalitis also the CSF results. There was history of aspirin ingestion or other drugs that suggested to RS. Progressive enlargement of the liver, higher SGOT and SGPT more than 3-fold, deep and deeper coma made think about RS. The limitation of this case is the absence of liver biopsy. About 25% of patients presenting in admission in deeper levels of coma (stages III to V) remain stable or worsen rapidly or slowly over the ensuing days as the disease runs its full course. Their illness is often complicated with multiorgan failure including refractory elevation of intracranial pressure, signs of herniation of brain tissue, sudden hypotension due to impaired cardiac function and/or arrythmias, sever electrolyte abnormalities due to inappropriate vasopressin secretion, renal failure, and neurogenic pulmonary edema.

The diagnostic criteria for Reye's syndrome are:

- Acute non-inflammatory encephalopathy with altered level of consciousness
- Hepatic dysfunction with a liver biopsy showing fatty metamorphosis or more than 3-fold increase in ALT, AST and/or ammonis levels.
- No other explaination for cerebral edema or hepatic abnormality.
- Cerebrospinal fluid (CSF) with 8 or fewer WBCs per cubic millimeter.
- Brain biopsy with cerebral edema inflammation.

Acute pancreatitis may complicate both mild and severe cases of Reye's syndrome and result in the sequestration of significant amounts o0f fluid in the abdomen and retroperitoneal space. It should be suspected when unexplained discrepancies exist in the fluid management of these patients. Therefore the routine monitoring serum amylase is recommended in all RS patients from time admission.

Starko, et al, During an outbreak of influenza A, seven patients with Reye's syndrome and 16 ill classmate control subjects were evaluated for characteristics of the patients' prodromal illness and the control subjects' illness and for medication usage. Patients during the prodrome and control subjects had similar rates of sore throat, coryza, cough, headache, and gastrointestinal complaints except for documented fever which occurred significantly more often in patients than in control subjects ($P = .05$). While medications which did not contain salicylate were taken as frequently by patients as control subjects, patients took more salicylate-containing medications than did control children ($P < .01$). All seven patients took salicylate whereas only eight of 16 control subjects did so ($P < .05$) Patients took larger doses of salicylate than did the entire control group ($P < .01$). When the eight control subjects who took salicylate were compared with the patients, the patients still tended to take larger doses ($P = .08$). Patients with fever took salicylate more frequently than control subjects with fever ($P < .01$). In addition, salicylate consumption was correlated with severity of Reye's syndrome ($P < .05$). It is postulated that salicylate, operating in a dose-dependent manner, possibly potentiated by fever, represents a primary causative agent of Reye's syndrome.

Arrowsmith, et al, The number of cases of Reye syndrome reported annually to the Centers for Disease Control and Prevention declined markedly between 1980 and 1985. In this article we present pharmaceutical marketing research data that suggest sharp decreases in the use and purchase of children's aspirin between 1980 and 1985. These trends appear to correspond to the decrease in reporting of Reye syndrome cases. Additionally, analysis of physician mentions of aspirin and acetaminophen for treating flu and chickenpox showed statistically significant trends toward increasing recommendations for use of acetaminophen. Trends in wholesale purchases of aspirin and acetaminophen by drug stores from 1979 through 1985 demonstrated a significant decline for the 81-mg children's aspirin tablet and an increase in purchases of children's acetaminophen products. Many factors may influence physician and parents' choice of analgesic/antipyretic medication, including information about Reye syndrome. Data suggest that a continuing decline in the use of aspirin for children may be accompanied by a continuing decline in the reported number of Reye syndrome cases.

To reduce the fever for the children most author suggest to give paracetamol and ibuprofen as well that has more less side effect compare to aspirin. When promoting paracetamol and ibuprofen it would be wise not to conceal their side effect- for example, the

hepatotoxicity of paracetamol, which can occur even at minor overdoses given during a few days.

Retrospective re-evaluation of surviving patients diagnosed with RS has revealed that many, if not most, of this patients have an underlying inborn error metabolism. Error include amino and organic acidopathies, urea cycle defects, disorders of carbohydrate metabolism, and fatty acid oxidation defects, which may mimic RS. This has led debate about the etiology of RS, including if it is truly distinct entity and not a variety of metabolic disorder. 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. In 2002 the ban on aspirin was raised to 16 years old.

Among the survival, recurrences of the disease are rare but have been reported. Some children had up to five repeat episodes of Acute Reye's syndrome, and turned out to have one of the metabolic disorder. We therefore urge that all the patients with recurrences be screened for an underlying inborn metabolism as previously mentioned.

SUMMARY

It has been reported a case of Reye's syndrome in 2 years 2 months old boy. The patients died after six days treatment in the hospital. The cause of Reye's syndrome is not clear. Epidemiology methods have established a statistical association between aspirin ingestion during an antecedent viral infection and Reye's syndrome, but they cannot establish causality non can they expose the biologic mechanism of the disease. Research must continue at the molecular level to determine how a limited set of specific viruses triggers the dramatic, universal, but potentially rapidly reversible damage of the liver cell mitochondrial function. If the effect is mediated through a specific protein structure, a genetic susceptibility, it will remain a biologic booby trap waiting to ensnare who knows how many of the xenobiotic molecules that lie in our future. There is no guarantee that there will not be another outbreak of Reye's syndrome.

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