

A Clinical Analysis of Ninety-Four Cases of Reye's Syndrome¹

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=Abstract=Ninety-four cases of Reye's syndrome, diagnosed clinically, were evaluated retrospectively, with special reference to epidemiology, clinical features and factors affecting the prognosis. Eighty per cent of cases were under two years of age. A preceding illness was identified in ninety cases, eighty-five of which had URI-like symptoms. Antecedent varicella had been present in three cases. Overall mortality was significantly higher in those with serum aspartate aminotransferase levels greater than 300 IU/L, lactic dehydrogenase greater than 750 IU/L, blood ammonia above 300 μ g/dl, white blood cell count over 20,000/mm³, and in those over 4 years of age. Mortality was also proportional to the stage of the disease on presentation; stage I-0%, stage II-29%, stage III-51% and stage IV-69%.

Key words: *Reye's syndrome, Prognosis*

INTRODUCTION

Since the original description of "encephalopathy and fatty degeneration of the viscera" by Reye and coworkers in 1963 (Reye *et al.* 1963), progress has been made in the understanding of this disease. The exact nature of the disease, however, is still far from clear.

Available evidence suggests that a primary mitochondrial injury results in multiple metabolic disturbances such as hyperammonemia, free fatty acidemia, lactic acidosis and dicarboxylic acidemia (Heubi *et al.* 1987). The metabolic abnormalities and the underlying mitochondrial injury which result in the observed pathophysiology is, as yet, incompletely understood (Zieve *et al.* 1974).

Despite multiple clues derived from clinical observations, the etiology of Reye's syndrome remains obscure. An antecedent viral illness such as upper respiratory illness, varicella or diarrheal illness, appears to be the common denominator underlying the development of Reye's syndrome. In addition, exposure to certain agents, such as salicylates, valproic acid, the unripe fruit of Akee

tree, margosa oil, etc, may produce clinical manifestations quite similar to Reye's syndrome (Heubi *et al.* 1987; Sinniah and Baskaran 1981); however, none of these agents is thought to represent the prime etiology of Reye's syndrome.

Reye's syndrome was originally described in terms of uniform pathologic changes of the viscera associated with rather characteristic clinical features which included acute encephalopathy and hepatic involvement. If effective measures are to be developed to treat this disorder early in its course, the disease must be diagnosed on clinical and biochemical grounds alone (Glasgow *et al.* 1972; Corey *et al.* 1976; CDC 1980). Compared to the epidemiological and clinical features of Reye's syndrome in the USA, contrasting features were observed in Asian population (Yamashita *et al.* 1984).

To test those observations, we reviewed eight years' experience on Reye's syndrome at Seoul National University Children's Hospital, with special reference to epidemiology, clinical symptoms and factors affecting prognosis.

MATERIALS AND METHODS

Patient selection was based primarily on the clinical criteria of CDC case definition (CDC 1980); 1) an acute noninflammatory encephalopathy

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documented clinically by an alteration in consciousness, that is, stage I or deeper encephalopathy, and if available, a record of the cerebrospinal fluid (CSF) containing ≤ 8 leukocytes per mm^3 or histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation, 2) evidence of hepatic involvement documented by either: a) a liver biopsy or autopsy specimen considered to be diagnostic of Reye's syndrome, or b) a three fold or greater rise in the levels of the serum aspartate aminotransferase (AST, GOT), alanine aminotransferase (ALT, GPT) or blood ammonia and 3) no other more reasonable explanation for the cerebral or hepatic abnormalities. Preceding illness was defined as that manifested within 14 days before onset of encephalopathy.

During the eight year study period, January 1979 to December 1986, one hundred and fifteen cases of suspected Reye's syndrome were treated. When reviewed retrospectively, ninety-four cases fulfilled the CDC clinical criteria. The remaining cases were excluded chiefly because of incomplete study, and those cases without CSF examination were also discarded. Of the ninety four cases studied, 6 cases had been examined histologically. Treatment was mainly conservative, including 10 per cent glucose solution, vitamin K, fresh frozen plasma, lactulose enema, oral Neomycin, and mannitol for control of increased intracranial pressure.

Coma staging criteria were based on the modification of those by Lovejoy *et al.* (1974); stage 0 -the patient is alert and awake, stage I-sleepy, lethargic and difficult to arouse, stage II-delirious and combative with purposeful or semipurposeful

movement, stage III-unarousable with decorticate posturing, stage IV-unarousable with decerebrate posturing and stage V-unarousable and areflexic with a flaccid paralysis and unresponsive pupils.

RESULTS

Epidemiological and clinical features

Annual incidence of cases steadily increased until 1985 followed by a sharp decline in 1986 (Fig. 1). Cases presented throughout the year, with peaks in May and December. These peaks parallel the periods of increased frequencies of upper respiratory tract infections in the community (Fig. 2). Peak incidence was observed in the 6 months to 2 years age group (Fig. 3). Seventy-five of the cases (80%) were less than 2 years of age. Only seven cases presented in children over 4 years of age. Mortality was higher in those over 4 years of age, as compared to those under 4 years of age (86% vs. 41%, $p < 0.025$). Male to female ratio was 50 to 44.

Preceding illness was evident in ninety cases (96%). Of these, eighty-five cases were preceded by URI-like symptoms, and three cases by varicella. Two cases presented after symptoms of gastroenteritis. No preceding illness was identified in four cases. The mean duration between the onset of the preceding illness and the onset of encephalopathy was 5.5 ± 3.0 days, ranging from 1 to 14 days.

Deranged consciousness, stage I or deeper, was identified in all cases. Generally the mortality rate increased as the stage of coma on admission worsened (Table 1); stage 0 (2 cases) 100%, stage

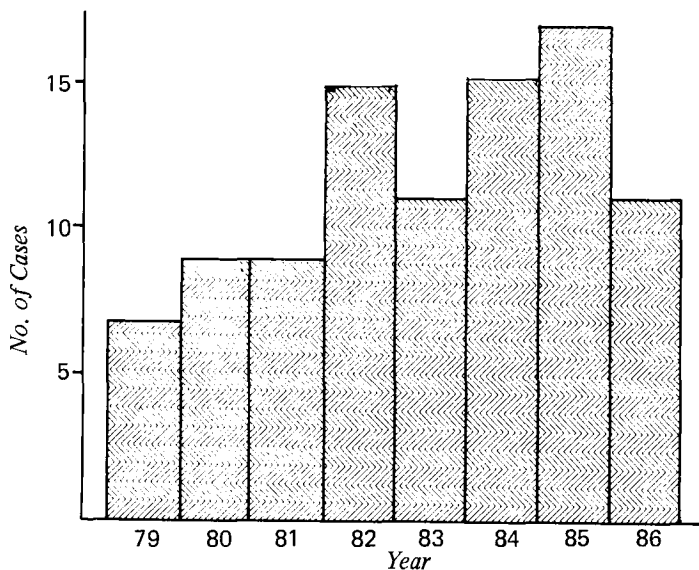


Fig. 1. Admitted cases of Reye's syndrome by year.

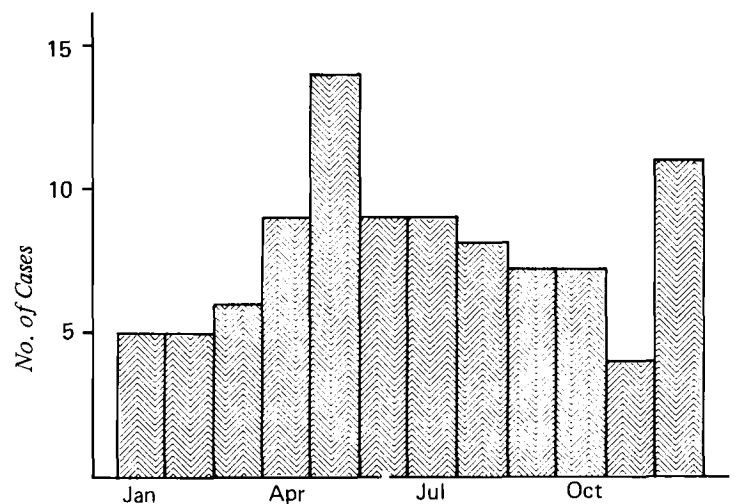


Fig. 2. Monthly distribution.

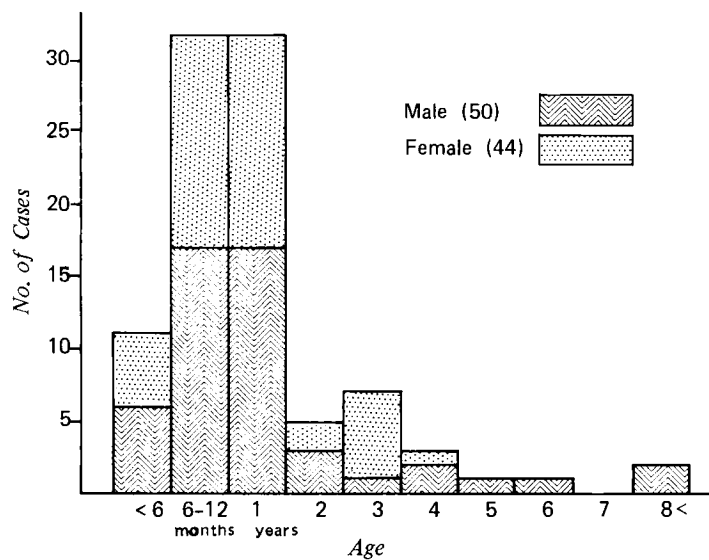


Fig. 3. Age and sex distribution

I (3 cases) 0%, stage II (35 cases) 29%, stage III (41 cases) 51%, stage IV (13 cases) 69%. For reasons unknown, two patients, both stage 0 on admission, progressed rapidly to death. One of them presented with renal failure, which was confirmed by autopsy. Vomiting was present in 89 per cent, fever in 72 per cent, hyperventilation in 61 per cent, and convulsion in 44 per cent. Hapatomegaly, of more than one finger breadth of palpable liver, was detected in 73 per cent.

Laboratory findings

Serum aspartate aminotransferase (AST) on admission ranged from 33 to 7698 IU/L (mean 404 IU/L). Peak AST values were above 60 IU/L in 92 cases (98%). Cases with AST level above 300 IU/L were associated with significantly higher mortality than those with below 300 IU/L (61% vs. 34%, $p < 0.025$).

Serum alanine aminotransferase (ALT) on admission ranged from 21 to 3580 IU/L (mean 393 IU/L). ALT values were elevated to 60 IU/L or more at admission or during hospitalization in 89 cases (95%). There was no significant correlation between AST level and mortality rate.

Blood ammonia levels over 150 μ g/dl during the disease course were observed in 78 cases (83%). Most had elevated ammonia blood levels on admission. Blood ammonia over 300 μ g/dl was significantly correlated with higher mortality (59% vs. 26%, $p < 0.005$).

Coagulation abnormality, judged as prothrombin time less than 60% of normal or prolongation of activated partial thromboplastin time more than 5 seconds was identified in 60(68%) of 88 patients. Patients with low prothrombin activity experienced

Table 1. Stage of coma on admission and mortality

Stage on admission	No. of cases	Mortality
0	2	2*(100%)
I	3	0 (0%)
II	35	10 (29%)
III	41	21 (51%)
IV	13	9 (69%)
V	—	—
Total	94	42 (45%)

*One presented as and died of acute renal failure, which was confirmed by autopsy.

a significantly higher mortality rate (56% vs. 28%, $p < 0.025$).

Serum glucose levels were less than 50 mg/dl in 26 (31%) of 85 patients. Of 68 patients in whom serum bilirubin levels were determined, values were over 1.5 mg/dl in 23 patients, the highest being 3.5 mg/dl, the next 2.8 mg/dl.

Serum lactic dehydrogenase (LDH) levels were elevated (over 250 IU/L) in 63 (95%) of 66 patients. The mortality of those with more than 750 IU/L was 56%, compared to 10% in the group with less than 750 IU/L, the difference was significant, $p < 0.005$. Serum phosphokinase (CPK) was elevated in 86% of those 63 in which it had been determined. There was no correlation between CPK and mortality. Peak white blood cell (WBC) counts were over 20,000/mm³ in 34 per cent of the patients, and was associated with higher mortality compared to those less than 20,000/mm³ (63% vs. 35%, $p < 0.025$).

The CSF cell counts were less than 8/mm³ in all cases except one, in which the cell count was 24/mm³. That single case was confirmed by histologic examination of the liver and brain.

Mortality and prognostic factors

The mortality of 71% in 1979 decreased to about 30% during the last three years. The over-all mortality rate during the study period was 45% (Fig. 4). As previously mentioned, mortality was higher in those with serum AST over 300 IU/L, LDH over 750 IU/L, blood ammonia over 300 μ g/dl, WBC count over 20,000/mm³, or age over 4 years. The mortality also increased as the clinical stage of the disease on admission advanced (Table 2).

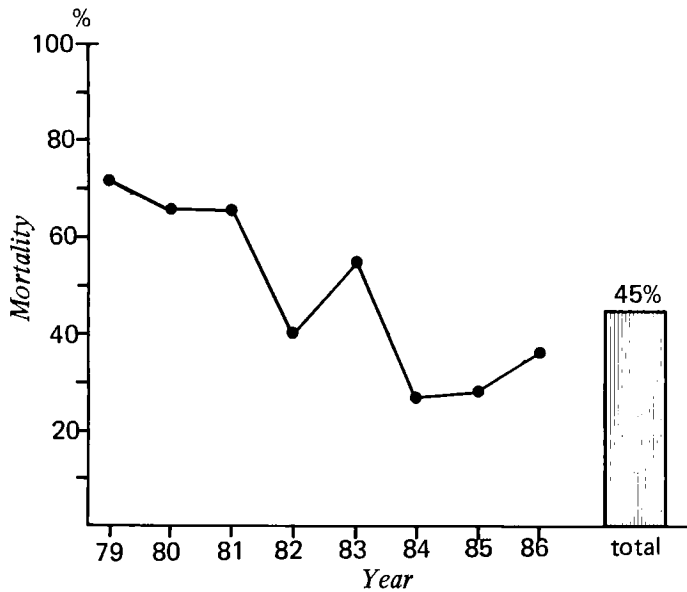


Fig. 4. Overall annual mortality change.

Immediate residual sequelae were observed in 6 of 52 survived patients, affecting 12% of the surviving group (Table 3). Two remained in comatous state. One had spastic hemiparesis, another one had tremor with brain infarction on computed tomography. Two had weakness of the extremities.

DISCUSSION

The diagnostic pathological changes in Reye's syndrome consist of cerebral edema without perivascular or meningeal inflammation, and fatty degeneration of the viscera, such as the liver, kidney and occasionally the myocardium and pancreas, without hepatocellular necrosis or significant inflammatory infiltrate (Reye *et al.* 1963). Clinically the non-inflammatory encephalopathy usually is documented by the symptoms of CNS involvement

Table 3. Immediate residual sequelae in 6 out of 52 survived patients

No.	Age	Sex	Sequelae
1	2 8/12	F	Comatous state
2	6/12	F	Comatous state
3	1	M	Spastic hemiparesis
4	6/12	M	Brain infarction with tremor
5	1 10/12	F	Upper extremity weakness
6	8 1/12	M	Lower extremity weakness

and normal CSF findings except occasional reduced glucose content. The characteristic microvesicular fatty metamorphosis of the liver can be confirmed only by biopsy or necropsy. The liver biopsy is not always possible because the hepatic lesions are frequently complicated by low prothrombin activity. Though some authors suggest percutaneous liver biopsy can be performed with minimal risk (Schubert 1975), most clinicians are reluctant to perform invasive procedures in critically-ill patients. As a result many attempts have been made to diagnose hepatic involvement biochemically (Glasgow *et al.* 1972; Corey *et al.* 1976; CDC 1980). As is the case with this study, the CDC criteria (1980) are the most commonly used.

The clinical definition is practical and believed to be sensitive, but recently the specificity of the hepatic involvement by clinical grounds as well as pathologic findings has been challenged (Bonnell and Beckwith 1986; Karena *et al.* 1987; Ko 1987).

In addition, the criteria for CNS involvement is also changing. The CDC criteria and the consensus conference at the National Institutes of Health (Dodge *et al.* 1981) classified the lowest level of

Table 2. Laboratory parameters with prognostic significance in Reye's syndrome

Parameters*	Criteria	Prevalence	Mortality	Significance
AST (IU/L)	< 300	56/94	19/56(34%)	p < 0.025
	≥ 300	38/94	23/38(61%)	
Ammonia(μg/dl)	< 300	43/94	11/43(26%)	p < 0.005
	≥ 300	51/94	31/51(59%)	
LDH (IU/L)	< 750	21/66	2/21(10%)	p < 0.005
	≥ 750	45/66	24/45(56%)	
WBC count(/mm ³)	< 20,000	62/94	22/62(35%)	p < 0.025
	≥ 20,000	32/94	20/32(63%)	
Prothrombin activity (% of normal)	> 60	43/86	12/43(28%)	p < 0.025
	≤ 60	43/86	24/43(56%)	

*Represent peak or lowest values during hospitalization.

Not significant correlation between mortality and ALT or CPK levels was found.

impaired consciousness recognized for Reye's syndrome (stage 1) as lethargy while still following verbal commands. But clinical investigators have described stage 0 or very mild Reye's syndrome cases in which the patients presented in an alert and wakeful state (Corey *et al.* 1977b), and Holtzauer *et al.* (1986) suggest that severe vomiting without consciousness disturbance be regarded as onset of encephalopathy. We also had 2 patients without change in consciousness on admission; however these patients subsequently developed changes in consciousness. The CDC criteria excludes patients > 8 WBC/mm³ in the CSF. However histologically proven cases of Reye's syndrome with CSF pleocytosis were reported in seven of forty-three in Glasgow *et al.*'s series (1972) and in four of 147 in Corey *et al.*'s series (1977a). The authors also experienced CSF pleocytosis in one of six histologically proven cases.

Differences in clinical characteristics of Reye's syndrome in the United States and Asian population have been noted (Yamashita *et al.* 1985). In the USA, the peak incidence is 5 to 15 years, with median age of 11 years in cases preceded by influenza B and 6 years in patients preceded by varicella (Corey *et al.* 1976). In Asia the peak incidence age is lower. Three types of antecedent illness in patients with Reye's syndrome have been identified; upper respiratory illness including influenza type B, varicella and gastrointestinal illness. In Asian population, a smaller proportion of cases are preceded by varicella, 3% in this series, compared to about 10% in the United States. The younger peak age may partly be explained by different antecedent illnesses compared to those in the USA. The incidence of fever and convulsion is higher in Asia than in the USA. A high rate of convulsions was observed only in infancy in the USA (Huttenlocher and Trauner 1978). It is interesting that the data from the United Kingdom has the same pattern of peak incidence age, similar type of antecedent illnesses and high rate of convulsion (Hall and Bellman 1981-1982).

Although the Reye's syndrome survival rate is increasing, mortality still remains high. The mortality in the first year of the study period was 71 per cent, but decreased to about 30 per cent in the latter part of the study period. There was no change in the management of the patients. The decreased mortality is thought to result from earlier detection of mild cases due to a higher index of suspicion, resulting in earlier therapeutic intervention. Some authors recommend intracranial pres-

sure monitoring (Berman *et al.* 1975). Exchange transfusion may or may not improve the survival rate (Bobo *et al.* 1975; Corey *et al.* 1977b).

Several factors are of prognostic value in Reye's syndrome. Mortality was significantly higher in those with serum AST over 300 IU/L, lactic dehydrogenase over 750 IU/L, blood ammonia over 300 μ g/dl, white blood cell count over 20,000/mm³, age over 4 years, or advanced stage of encephalopathy on admission. Previous reports postulate, as prognostic predictors, ammonia levels (Fitzerald *et al.* 1982; Huttenlocher 1972; Corey *et al.* 1977b), stage of encephalopathy on admission (DeVivo 1975; Corey *et al.* 1977b), CPK (Corey *et al.* 1977a), GOT and prothrombin activity (Glasgow *et al.* 1972), age less than 12 months (Mowat 1983), or over 5 years (Hall and Bellman 1985). The reason why the mortality is significantly correlated with peak AST but not with peak ALT is not clear. AST values are usually maximum at admission while ALT values peak later in the hospitalization, and high values of peak ALT were frequently observed in surviving patients. This fact may partly explain the result.

Complete recovery may be expected in the majority of patients who survive the acute illness. However, some children who experienced coma may suffer brain damage resulting in developmental delay, motor impairment, or mental retardation. Immediately after the illness, residual sequelae were observed in 12% of the survived patients. Sometimes, distractibility, inattention, and memory problems may occur on long-term follow-up (Dodge *et al.* 1981). Some authors suggest that residual neurologic deficit is more likely to occur in patients of younger age (Corey *et al.* 1977b). Davidson *et al.* (1975) found that seven of 11 patients with Reye's syndrome demonstrated either neurologic or psychomotor abnormalities in follow-up testing two years after their illness. Three of 4 patients under 1 year of age were retarded. Thus, further evaluation of the relationship between neurologic and psychologic deficits in Reye's syndrome is needed.

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=국문초록=

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1963년 Reye 등이 '뇌증 및 내장의 지방 변성'을 기술한 이래 이 질환에 대한 많은 연구가 되어왔으나 아직 이의 확실한 정체가 밝혀지지 않은 상태이며, 아시아인에서의 여러가지 임상상이 서구인에 비해 다소의 차이가 있는 것으로 보고되고 있다. 저자들은 1979년부터 1986년까지 8년간 경험한 94예의 Reye 증후군 환아들의 역학, 임상상, 예후 및 예후에 영향을 미치는 요소 등을 분석하였다. 94예중 75예(80%)가 2세 이하의 소아였으며, 생후 6개월에서 2세 사이에 발생빈도가 가장 높았다. 선행 질환은 90예에서 인지되었으며, 그중 상기도 감염 증상이 85예, 수두가 3예, 위장관염 증상이 2예 이었다. 증상으로는 의식장애(100%), 구토(89%), 발열(72%), 과호흡(61%), 경련(44%)의 순이었고 간비대가 73%에서 발견되었다. 1979년의 사망율이 71%이었으나 1984-1986년에는 약 30%로 감소하여 전체 사망율은 45%이었다. 후유증은 생존한 환아 52예중 6예(12%)에서 관찰되었다. 질병의 경과중에 혈청 AST가 300 IU/L, LDH 750 IU/L, 암모니아 300 $\mu\text{g}/\text{dl}$ 또는 말초혈액 백혈구수가 20,000/ mm^3 이상으로 증가된 경우에는 예후가 불량하였으며, 4세 이상의 소아는 4세 이하의 소아에 비해 사망율이 높았다. 또한 입원시 의식장애의 정도가 심할수록 사망율이 높았다.