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## REYE'S SYNDROME IN THE UNITED STATES FROM 1981 THROUGH 1997

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### ABSTRACT

**Background** Reye's syndrome is characterized by encephalopathy and fatty degeneration of the liver, usually after influenza or varicella. Beginning in 1980, warnings were issued about the use of salicylates in children with those viral infections because of the risk of Reye's syndrome.

**Methods** To describe the pattern of Reye's syndrome in the United States, characteristics of the patients, and risk factors for poor outcomes, we analyzed national surveillance data collected from December 1980 through November 1997. The surveillance system is based on voluntary reporting with the use of a standard case-report form.

**Results** From December 1980 through November 1997 (surveillance years 1981 through 1997), 1207 cases of Reye's syndrome were reported in patients less than 18 years of age. Among those for whom data on race and sex were available, 93 percent were white and 52 percent were girls. The number of reported cases of Reye's syndrome declined sharply after the association of Reye's syndrome with aspirin was reported. After a peak of 555 cases in children reported in 1980, there have been no more than 36 cases per year since 1987. Antecedent illnesses were reported in 93 percent of the children, and detectable blood salicylate levels in 82 percent. The overall case fatality rate was 31 percent. The case fatality rate was highest in children under five years of age (relative risk, 1.8; 95 percent confidence interval, 1.5 to 2.1) and in those with a serum ammonia level above 45  $\mu\text{g}$  per deciliter (26  $\mu\text{mol}$  per liter) (relative risk, 3.4; 95 percent confidence interval, 1.9 to 6.2).

**Conclusions** Since 1980, when the association between Reye's syndrome and the use of aspirin during varicella or influenza-like illness was first reported, there has been a sharp decline in the number of infants and children reported to have Reye's syndrome. Because Reye's syndrome is now very rare, any infant or child suspected of having this disorder should undergo extensive investigation to rule out the treatable inborn metabolic disorders that can mimic Reye's syndrome. (N Engl J Med 1999;340:1377-82.)

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**R**EYE'S syndrome is an acute illness characterized by encephalopathy and fatty degeneration of the liver, and it occurs almost exclusively in children. Although patients with these manifestations had been reported sporadically since 1929,<sup>1</sup> Reye's syndrome as a distinct clinicopathological entity was first described in 1963 by Reye et al. in Australia.<sup>2</sup> In the same year, Johnson et al. in the United States described several cases of Reye's syndrome that occurred during an outbreak of influenza B.<sup>3</sup> The onset of Reye's syndrome is heralded by profuse vomiting and varying degrees of neurologic impairment, including fluctuating personality changes and deterioration in consciousness. As the encephalopathy becomes more severe, extreme irritability, agitation, confusion, delirium, and coma may develop. Numerous metabolic derangements have been identified in affected patients, including hyperammonemia and elevated levels of alanine aminotransferase and aspartate aminotransferase.

Various inborn metabolic disorders, which require extensive laboratory testing for diagnosis, can present with manifestations that mimic those of Reye's syndrome, and clinical differentiation is often difficult. The majority of these inherited disorders are specific enzymatic defects that commonly become evident before the age of three years.<sup>4-7</sup> These disorders are characterized by recurrent episodes, the presence of the disorder in siblings, frequent hypoglycemia, cardiac enlargement, and muscle weakness. The most consistent distinguishing features of Reye's syndrome on electron microscopy are ultrastructural changes in liver tissue, specifically the proliferation of smooth endoplasmic reticulum and peroxisomes and the pres-

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ence of enlarged and pleomorphic mitochondria with loss of dense granules.<sup>7,8</sup> In enzymatic defects with Reye's syndrome-like manifestations, in contrast, the mitochondria are normal in size and appearance.

Although the precise cause of Reye's syndrome is unknown, it is often preceded by a viral syndrome, usually varicella, gastroenteritis, or an upper respiratory tract infection such as influenza.<sup>9</sup> Studies have demonstrated a strong epidemiologic association between the ingestion of aspirin during antecedent varicella or influenza-like illnesses and the subsequent development of Reye's syndrome.<sup>10-14</sup> Beginning in 1980, as a result of these reports, the Centers for Disease Control and Prevention (CDC) cautioned physicians and parents not to use salicylates in children with varicella or influenza-like illnesses.<sup>15-17</sup> An advisory was also issued by the surgeon general of the United States in June 1982,<sup>18</sup> and a warning label was required for all aspirin-containing medications beginning in 1986.<sup>19</sup>

In this article, we describe the epidemiologic characteristics of patients with Reye's syndrome and the trends in cases reported to the National Reye Syndrome Surveillance System (NRSSS) from December 1, 1980, through November 30, 1997.

## METHODS

### Surveillance for Reye's Syndrome

A system of national surveillance for Reye's syndrome was established during the period from December 15, 1973, through June 30, 1974, to monitor the incidence of Reye's syndrome during an anticipated epidemic of influenza B. The CDC reinstated national surveillance for Reye's syndrome in December 1976 and has continued it through the NRSSS ever since. The NRSSS is a voluntary passive-surveillance system in which practicing physicians and hospital personnel report cases of Reye's syndrome to local or state health departments or, in a few states, directly to the CDC. A standard case-report form is used to collect information on patients, including demographic characteristics, antecedent illness, diagnostic criteria, levels of consciousness, laboratory data, and the outcome of the illness. The surveillance year for Reye's syndrome begins on December 1 and ends on November 30 in order to reflect the influenza season.

### Case Definition

The CDC defines a case of Reye's syndrome as one in which there is acute, noninflammatory encephalopathy, manifested clinically by alterations in the level of consciousness and documented, when such results are available, by the measurement of 8 or fewer leukocytes per cubic millimeter of cerebrospinal fluid or by the presence of cerebral edema without perivascular or meningeal inflammation in histologic sections of the brain. The encephalopathy must be associated with either fatty metamorphosis of the liver, diagnosed by biopsy or at autopsy, or a tripling (or a greater increase) in the levels of alanine aminotransferase, aspartate aminotransferase, or ammonia in serum. There must, moreover, be no other more reasonable explanation of the cerebral or hepatic abnormalities.

A clinical staging system is used in the NRSSS (Table 1). Patients with a clinical history and laboratory abnormalities compatible with Reye's syndrome, but without central nervous system symptoms, are classified as at stage 0. Such patients do not fulfill the CDC case definition, because this definition requires symptoms of encephalopathy. Also in the NRSSS, an additional category,

**TABLE 1. CLINICAL STAGING OF LEVEL OF CONSCIOUSNESS IN THE NATIONAL REYE SYNDROME SURVEILLANCE SYSTEM.**

STAGE	CHARACTERISTICS
0	Alert, wakeful
1	Difficult to arouse, lethargic, sleepy
2	Delirious, combative, with purposeful or semipurposeful motor responses
3	Unarousable, with predominantly flexor motor responses, decorticate
4	Unarousable, with predominantly extensor motor responses, decerebrate
5	Unarousable, with flaccid paralysis, areflexia, and pupils unresponsive
6	Treated with curare or equivalent drug, and therefore unclassifiable

made up of patients to whom curare or an equivalent drug had been administered and who were therefore unable to be classified, is used for patients who had been given medications that would interfere with the evaluation of the level of consciousness.

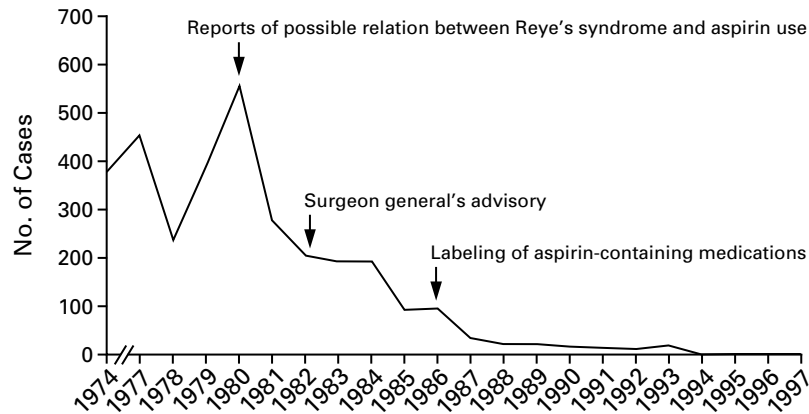
### Statistical Analysis

Only patients under 18 years of age who fulfilled the CDC case definition for Reye's syndrome were included in the statistical analysis. Variations in the number of patients in the denominator are due to nonresponse to questions on the case-report form or to responses of "unknown." The chi-square statistic was used to test for an association between race and the distribution of cases according to age group and for an association between detectable blood salicylate levels and period. We compared the characteristics and laboratory results of patients who died with those of survivors in order to identify associated risk factors; relative risks and 95 percent confidence intervals were calculated. Multiple logistic-regression analysis was used for the further examination of risk factors that were significantly associated with increased case fatality by fitting a series of hierarchical models.<sup>20</sup>

## RESULTS

From December 1, 1980, through November 30, 1997 (surveillance years 1981 through 1997), a total of 1207 cases of Reye's syndrome in patients under 18 years of age were reported to the CDC. A dramatic decline in the number of reported cases of Reye's syndrome was observed during this 17-year period (Fig. 1). A peak of 555 cases were reported in surveillance year 1980. In 1985 and 1986, there was an average of just under 100 reported cases per year. From 1987 through 1993, no more than 36 cases were reported each year, and from 1994 through 1997, no more than 2 cases were reported each year.

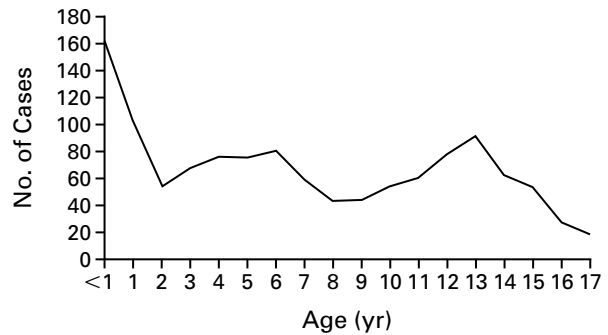
The sex of 1190 of the 1207 patients was reported; 618 (51.9 percent) were girls. Of the 1170 patients whose race was reported, 1083 (92.6 percent) were white, 59 (5.0 percent) were black, 24 (2.1 percent) were Asian or Pacific Islander, and 4 (0.3 percent) were American Indian or Alaskan Native.



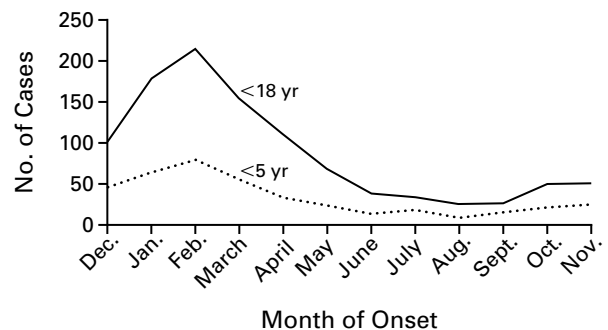
**Figure 1.** Number of Reported Cases of Reye's Syndrome in Relation to the Timing of Public Announcements of the Epidemiologic Association of Reye's Syndrome with Aspirin Ingestion and the Labeling of Aspirin-Containing Medications.

The median age was six years, and the mean age was seven years. One hundred sixty-three of the patients (13.5 percent) were infants less than 1 year old, 300 (24.9 percent) were children 1 to 4 years old, and 646 (53.5 percent) were school-age children 5 to 14 years old; the remainder were 15 through 17 years of age (Fig. 2). Thirty-three of the 59 black patients with Reye's syndrome (55.9 percent) were between 1 and 17 years of age, as compared with 957 of the 1083 white patients (88.4 percent,  $P < 0.01$ ). The lower proportion of black patients who were 1 through 17 years of age reflected the considerably lower incidence of Reye's syndrome in this age group among blacks than among whites, despite the similar incidence of Reye's syndrome among black and white infants (data not shown).

Of 1160 patients for whom data on antecedent illness were available, at least one episode of illness was reported for 1080 patients (93.1 percent) during the three weeks before the onset of Reye's syndrome. Respiratory illnesses, the most commonly reported type of illness, occurred in 733 of 999 patients (73.4 percent), followed by varicella in 209 of 1006 patients (20.8 percent), diarrhea in 127 of 896 patients (14.2 percent), and other illnesses with rash in 49 of 929 patients (5.3 percent). Except for the occurrence of seven cases in one county in 1981, no more than four cases of Reye's syndrome were reported in any single county during any respiratory-virus season (December through April). A seasonal variation in the overall number of cases of Reye's syndrome reported was observed in most years, with a peak from December through April; a similar seasonal pattern was observed for patients less than five years of age (Fig. 3). Before 1990 the incidence of Reye's syndrome was higher in years with epidemics of influenza B than in years with epidemics of influenza



**Figure 2.** Number of Reported Cases of Reye's Syndrome According to Age at Onset, December 1980 through November 1997 (Surveillance Years 1981 through 1997).



**Figure 3.** Seasonal Variation in the Number of Reported Cases of Reye's Syndrome in Patients under 18 Years of Age and in Those under 5 Years of Age, December 1980 through November 1997 (Surveillance Years 1981 through 1997).

A(H3N2) or influenza A(H1N1), but this association was not found subsequently.

Salicylate levels in blood obtained within 48 hours after hospital admission were reported for 531 of 953 patients with Reye's syndrome (55.7 percent); 435 (81.9 percent) had detectable levels of salicylates. The proportion of patients with detectable blood salicylate levels was significantly higher during the period from 1981 through 1986 (392 of 467 patients tested [83.9 percent]) than during the period from 1987 through 1997 (43 of 64 patients tested [67.2 percent],  $P < 0.01$ ). Fourteen of 361 patients with Reye's syndrome (3.9 percent) were reported to have taken aspirin regularly as long-term treatment for illness; 10 of these patients (71.4 percent) had juvenile rheumatoid arthritis. A previous episode of Reye's syndrome, diagnosed by a physician, was reported in 4 of 1076 patients (0.4 percent) and the presence of Reye's syndrome in a sibling or a blood relative in 18 of 613 patients (2.9 percent) for whom this information was available. These prevalence rates are much higher than would be expected in the general population under 18 years of age.

Nine hundred fifty-five of 1178 patients with Reye's syndrome (81.1 percent) had a stage 0, 1, or 2 illness at the time of hospital admission. Although a small proportion of patients had disease classified as stage 2 through 5 at admission, 428 of 931 patients (46.0 percent) had stage 3, 4, or 5 illness at some point. Higher stages of illness at admission were associated with a poor prognosis; 16 of 90 patients (17.8 percent) with stage 0 illness at admission died, for example, as compared with 69 of 77 patients (89.6 percent) with stage 5 illness ( $P < 0.01$ ) (Table 2).

Of the 1134 patients (94.0 percent) for whom the final outcome of Reye's syndrome was reported, 355 patients died, for an overall case fatality rate of 31.3

percent. Children less than five years of age had a significantly higher case fatality rate (186 of 435, or 42.8 percent), than children five years of age or more (169 of 699, or 24.2 percent; relative risk, 1.8; 95 percent confidence interval, 1.5 to 2.1). Patients with serum ammonia levels above 45  $\mu\text{g}$  per deciliter (26  $\mu\text{mol}$  per liter) had a significantly higher case fatality rate (260 of 908, or 28.6 percent) than patients with ammonia levels at or below 45  $\mu\text{g}$  per deciliter (7 of 83, or 8.4 percent; relative risk, 3.4; 95 percent confidence interval, 1.9 to 6.2). The case fatality rate was also significantly increased by the presence of diarrhea during the antecedent illness, a serum glucose level of less than 60 mg per deciliter (3.3 mmol per liter), and black race. After logistic-regression analysis, however, an age of less than five years and a serum ammonia level above 45  $\mu\text{g}$  per deciliter remained significantly associated with an increased risk of death ( $P < 0.01$ ). Residual neurologic complications were reported in 76 of the 779 living patients (9.8 percent); the complications were mild in 54 of these patients (6.9 percent) and severe in 22 patients (2.8 percent). Patients with serum ammonia levels above 45  $\mu\text{g}$  per deciliter had a significantly higher risk of neurologic complications (70 of 648, or 10.8 percent) than patients with levels at or below 45  $\mu\text{g}$  per deciliter (2 of 76, or 2.6 percent; relative risk, 4.1; 95 percent confidence interval, 1.2 to 14.0). Complete recovery was reported in 703 (62.0 percent) of the 1134 patients with Reye's syndrome whose outcomes were known.

## DISCUSSION

There has been a dramatic decline in the number of reported cases of Reye's syndrome since 1980. This decline followed reports of the association of Reye's syndrome with the use of aspirin during antecedent varicella and influenza-like illness,<sup>10-12,16,17</sup> the issuance of an advisory by the surgeon general,<sup>18</sup> and the labeling of aspirin-containing medications with a warning about the risk of Reye's syndrome.<sup>19</sup> Studies have documented a decline in the rate of use of aspirin in children after these precautionary measures were taken.<sup>21-23</sup>

The peak in reported cases of Reye's syndrome from December through April correlates with the seasonal occurrence of viral upper respiratory tract infections, particularly influenza, in the United States. This seasonal occurrence of Reye's syndrome has become less obvious since 1990, indicating that respiratory infections alone are not sufficient to cause distinct seasonal peaks in the numbers of cases of Reye's syndrome.

Although the overall decline in the number of cases of Reye's syndrome reported to the NRSSS is clear, the absolute number of cases should — as in any passive-surveillance system — be interpreted cautiously. A slight decrease in the sensitivity of re-

**TABLE 2.** OUTCOME OF PATIENTS WITH REYE'S SYNDROME ACCORDING TO THEIR STAGE OF ILLNESS AT ADMISSION.\*

STAGE	OUTCOME				TOTAL
	COMPLETE RECOVERY†	MILD NEUROLOGIC SEQUELAE	SEVERE NEUROLOGIC SEQUELAE	DEATH†	
		number (percent)			
0	73 (81.1)	1 (1.1)	0	16 (17.8)	90
1	318 (76.6)	15 (3.6)	4 (1.0)	78 (18.8)	415
2	253 (64.4)	29 (7.4)	8 (2.0)	103 (26.2)	393
3	36 (45.0)	3 (3.8)	2 (2.5)	39 (48.8)	80
4	12 (23.5)	4 (7.8)	4 (7.8)	31 (60.8)	51
5	3 (3.9)	1 (1.3)	4 (5.2)	69 (89.6)	77

\*The analysis includes only patients for whom the stage of illness at admission and the outcome were known.

† $P < 0.01$  by the chi-square test for linear trend.

porting to the NRSSS, particularly during the 1990s, might have occurred, but not enough to account for the dramatic decline described in this summary. A trend toward a decline in hospitalizations for Reye's syndrome from 1991 through 1994 was shown by a recent review of hospital-discharge data from approximately one third of all nonfederal general acute care hospitals and all specialized children's hospitals in the United States (Sullivan KM: unpublished data). This review indicated a decline in the number of hospitalizations for Reye's syndrome from 30 in 1991 to 15 in 1994. On the basis of this study, the nationwide annual rate of hospitalizations for Reye's syndrome during 1994 was estimated as 0.06 per 100,000 persons under 18 years of age. This is likely to be an overestimate, because the patients included in the hospital-discharge data were not known to fulfill the CDC case definition for Reye's syndrome. In contrast, for the years preceding the reports of the association of Reye's syndrome with aspirin use, population-based studies suggested an average annual incidence of Reye's syndrome of approximately 1 case per 100,000 persons under 18 years of age.<sup>24,25</sup> Our data are consistent with those from the British Isles, where a warning issued in June 1986 against the use of aspirin in children resulted in an overall decline in reported cases of Reye's syndrome and a significant reduction in cases that, according to a scoring system, are believed to represent true Reye's syndrome.<sup>26</sup>

According to NRSSS data, 14 of 361 patients with Reye's syndrome for whom data on aspirin use were available (3.9 percent) had regularly taken salicylate-containing medications for illnesses such as juvenile rheumatoid arthritis and Kawasaki's disease. Several studies have documented a higher attack rate of Reye's syndrome among children taking salicylates for juvenile rheumatoid arthritis.<sup>27,28</sup> Similarly, children taking higher doses of aspirin have been shown to be at increased risk for Reye's syndrome.<sup>29</sup> These findings underscore the importance of giving special attention to the care of patients with conditions that require the long-term administration of aspirin, such as Kawasaki's disease and juvenile rheumatoid arthritis. Vaccination against influenza and varicella should be offered to these patients in accordance with the recommendations of the Advisory Committee on Immunization Practices.<sup>30</sup> Their care givers should also be informed about the risks of long-term aspirin treatment and trained to recognize the early symptoms of Reye's syndrome so that aspirin can be promptly withdrawn if Reye's syndrome is suspected.

Inborn metabolic disorders that mimic Reye's syndrome may lead to misdiagnosis, particularly in children younger than three years of age. As the incidence of Reye's syndrome decreases, manifestations that resemble those of Reye's syndrome are increasingly likely to be due to inborn metabolic disorders.

Rigorous testing of patients with such signs and symptoms is indicated, either to confirm the diagnosis of Reye's syndrome or to identify specific enzymatic defects. Histologic examination of a liver-biopsy specimen should be performed and preferably reviewed by a pathologist experienced in recognizing electron-microscopical features of Reye's syndrome. The patient's family history of similar illness and precipitating factors such as changes in diet, prolonged fasting, unusual odor of the urine, or stress-related events, which are more common in persons with inborn metabolic disorders, may provide some clues for clinical decision making. The early detection of potentially treatable inborn metabolic disorders may prevent subsequent serious, life-threatening complications.

The decline in the incidence of Reye's syndrome that began soon after the public reports of the epidemiologic association of Reye's syndrome with aspirin demonstrates the importance of disseminating timely preventive messages to the public. Reye's syndrome, a severe neurologic disease that causes death or long-term neurologic sequelae in about one third of patients, was shown to be epidemiologically associated with the ingestion of aspirin, a widely used analgesic and antipyretic agent. The subsequent publicity about this association was critical to the success in reducing the occurrence of Reye's syndrome and its associated neurologic complications and in preventing the deaths of many children.

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