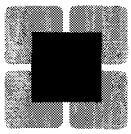

Reye's syndrome: a case control study of medication use and associated viruses in Australia

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■ The records of 49 cases of Reye's syndrome at three pediatric hospitals in Australia are compared with 94 controls. The diagnosis of Reye's syndrome was confirmed pathologically in 42 of 49 cases (86%). Aspirin or salicylate ingestion occurred in only 4 (8%), and paracetamol (acetaminophen) ingestion in 12 (24%) ($P>0.05$ by chi-square analysis). Of the controls, 3 (3%) had taken aspirin and 39 (41%) had taken paracetamol. Associated viruses included paramyxoviruses, picornaviruses, reoviruses, adenoviruses, and occasional varicella-zoster (herpesvirus). No influenza A or B viruses were recovered from any patient. This case control study of Reye's syndrome in Australia confirmed a lack of association between aspirin ingestion and the development of Reye's syndrome.

□ INDEX TERM: REYE'S SYNDROME □ CLEVE CLIN J MED 1990; 57:323-329

OUR previously published study of Reye's syndrome (RS) in Australia[1] found no association between aspirin ingestion and the development of RS. These cases were from a single hospital (The Children's Hospital, Camperdown) between 1973 and 1982, and there was a 90% pathologic confirmation of the diagnosis.

A criticism of that study was its lack of controls, despite our use of national pharmaceutical sales data that showed little or no use of pediatric aspirin over the period of the study, and despite the domination of the pediatric analgesic and antipyretic market in Australia for more than 25 years by paracetamol (acetaminophen). Data were also presented showing that RS was as common in Australia as in the United States, despite a lack of association with the use of aspirin.

In this report, our previous data are expanded to a total of 49 cases of RS, and data are presented on 94 controls matched for age, date seen at the hospital, and symptoms. Data are also presented on medication use and associated viruses.

METHODS

All cases of RS occurring at three major pediatric hospitals in Australia (The Children's Hospital, Camperdown, New South Wales; the Royal Children's Hospital, Melbourne, Victoria; and the Prince of Wales Children's Hospital, Randwick, New South Wales) between 1972 and 1986 were retrieved from the medical records departments at each hospital. That department

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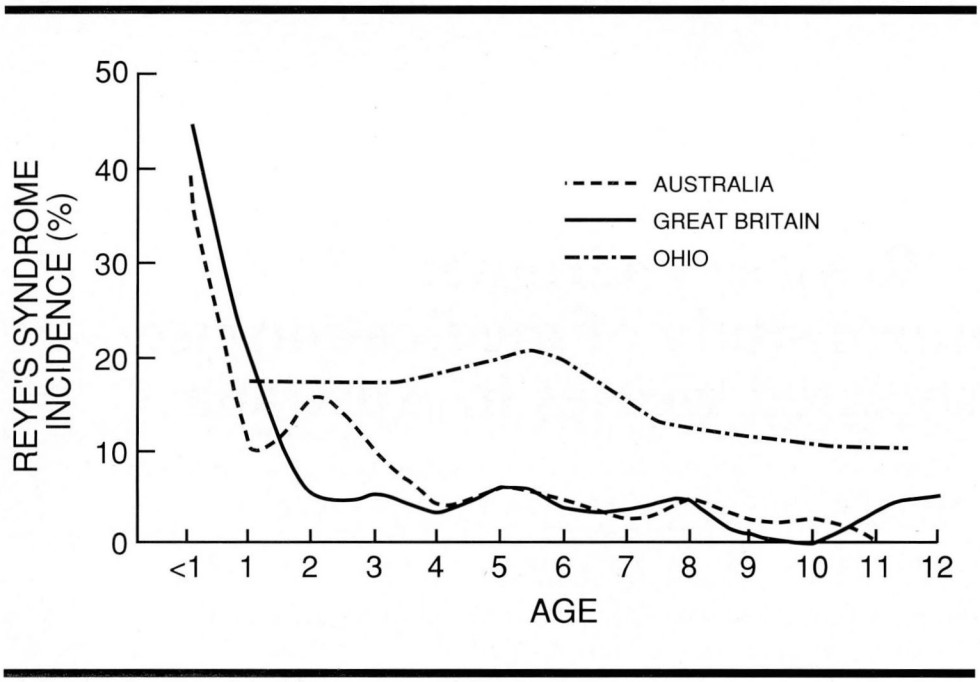

FIGURE 1. Age distribution of Reye's syndrome in Australia compared with Great Britain[4] and Ohio[5].

also provided one to three controls for each case, consisting of children of similar age and the same sex with similar symptoms who were seen at the casualty department or admitted to the hospital within 48 hours of the RS case. Two controls were requested for each case; occasionally only one control could be found, and sometimes three controls were provided. Hospital and casualty department controls were used because of the ease of obtaining the necessary data. If the patient with RS initially had symptoms of upper respiratory tract infection, controls with these symptoms were sought. If the prodromal illness in the RS case was gastrointestinal, controls with gastrointestinal symptoms were obtained. The records were reviewed for medical histories, laboratory studies, medication histories, toxicology screens and drug levels, viral titers, and viral isolation studies.

RS cases were required to meet three criteria: (1) acute noninflammatory encephalopathy that was documented clinically by an alteration in consciousness, and, if available, a record of cerebrospinal fluid containing eight leukocytes or fewer per microliter, or by histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation; (2) hepatopathy documented by liver biopsy or autopsy considered to be diagnostic of RS, or by a threefold or greater increase in the levels of SGOT, SGPT, or serum ammonia; and (3) no more likely an explanation for the cerebral or hepatic abnormalities.[2]

Paired t-tests and chi-square analysis were used for statistical analysis.

RESULTS

Histories of medication use in 49 RS cases and 94 controls (*Table 1*) showed a lack of association between the ingestion of aspirin or salicylates and the development of RS. No statistically significant association was found between aspirin or acetaminophen ingestion and the development of RS ($p > 0.05$ by chi-square analysis). Other medications taken by more than one RS or control patient included antibiotics (ampicillin, penicillin, erythromycin, and trimethoprim-sulfamethoxazole), an antihistamine (dexchlorpheniramine), a decongestant (pseudoephedrine), and an antiemetic (prochlorperazine).

Among 143 patients, 22 had drug or toxicology screens that confirmed their medication histories. One patient had a salicylate level of 0.67 μmol/L, and another had a salicylate level of 1.6 μmol/L (therapeutic range: 1.0 to 2.0); both had a history of aspirin ingestion. One patient with a history of paracetamol ingestion had a paracetamol level of 100 mmol/L. One patient who had a salicylate level of 0.013 μmol/L, despite a negative history for salicylate ingestion, was presumed to have a false positive test result for ketones.[3]

Despite suggestions that chart review is not an accurate method of determining medication histories, our experience was just the opposite. In 36 of 49 (73%) RS cases, the medication history was specifically positive or negative about salicylate and acetaminophen ingestion. In only 11 RS cases was the broad generalization of "no medications taken" stated, and most of these cases were infants where such a history is likely. Certainly, aspirin ingestion was highly unlikely in these infant cases because a liquid form of aspirin does not exist. In 22 cases, amino acid chromatography was performed on blood

TABLE 1
MEDICATION USE IN REYE'S SYNDROME CASES AND CONTROLS

Medications	Cases N = 49 (%)	Controls N = 94 (%)
Acetylsalicyclic acid	4 (8)	3 (3)
Acetaminophen	12 (24.5)	39 (41.5)
Ampicillin	10 (20)	12 (13)
Penicillin	7 (14)	4 (4)
Erythromycin	4 (8)	6 (6)
Dexchlorpheniramine	3 (6)	3 (3)
Prochlorperazine	3 (6)	3 (3)
Trimethoprim-sulfamethoxasole	2 (4)	0 (0)
Pseudoephedrine	2 (4)	3 (3)
No medications	16 (33)	26 (28)

TABLE 2
ASSOCIATED VIRUSES IN REYE'S SYNDROME CASES AND CONTROLS

Viruses	Cases (N = 49)	Controls (N = 94)
Myxoviruses		
Influenza A or B	0	1 (a)
Paramyxovirus		
Parainfluenza	2 (both a)	1 (a)
Respiratory syncytial virus	3 (all b)	10 (all b)
Measles, rubeola	0	1 (b)
Herpesviruses		
Varicella zoster	2 (both a)	2 (both a)
Picornaviruses		
Echo, rhino, entero, Coxsackie	6 (all b)	6 (all b)
Reovirus		
Rota, reo	3 (1 a, 2 b)	5 (4 a, 1 b)
Adenovirus	3 (all b)	12 (all b)
Dual virus		
Picorna, myxo, reo, adeno	5 (all b)	1 (b)

a = viral titers; b = direct isolation of virus.

and/or urine to evaluate inborn errors of metabolism.

The age distribution of the RS cases (*Figure 1*) was compared with data from Great Britain, 1981 to 1983[4] and from the state of Ohio in the United States for 1966 to 1976.[5]

Of the 49 RS cases in Australia, 42 (86%) had pathologic confirmation of the diagnosis by liver biopsy or postmortem examination, which demonstrated microvesicular fatty changes in the liver. Fatty infiltration occurred not only in the liver but also in other organs, including the pancreas, kidney, and heart. Encephalopathy was demonstrated in 42 (86%) of cases with normal cerebrospinal fluid, and 22 (45%) had histologic confirmation of RS encephalopathy.

Incidence figures for RS in Australia can be calculated from the number of cases found in hospital records in Melbourne and Sydney and from data on the pediatric population (ages 0 to 14 years) in these cities.[6] In Sydney (with a pediatric population of 1,259,794 in New South Wales), 25 cases were seen over a 13-year period, for 1.5 cases per million children per year. Melbourne (with a population of 937,142 children in the state of Victoria) had 24 cases in 15 years, for an incidence of 1.7 cases per million children per year. These incidence figures from Australia must be extrapolated, since all of these children were diagnosed as Stage II or greater and were admitted to pediatric intensive care units; the US data included Stage I figures as well.

Using only pathologically proven cases and the incidence-estimating technique of Lichtenstein and associates,[7] it can be estimated that the incidence of RS was 5.3 cases per million children per year in Sydney and 6.0 cases per million per year in Melbourne. These figures are lower than the 35 cases per million estimated by Lichtenstein and colleagues[7] for Cincinnati, Ohio, but they are higher than the average yearly incidence in the United States of 3 cases per million children (ages 0 to 17 years), based on data from the Centers for Disease Control.

Of the 49 RS cases in Australia, 23 died, for a 47% mortality rate.

Viral studies, both cultures and titers, were obtained on a number of the cases and controls (*Table 2*). Evidence of influenza A or B infection was not found in any RS case in Australia. Occasional varicella cases were associated with RS in Australia, just as in the United States.

When the distribution of cases by year in Australia was compared with the US data by year[2] (*Figure 2*), similarities were evident.

DISCUSSION

RS was formally described in 1963 as an acute encephalopathy with fatty degeneration of the viscera.[8] Although there were unsubstantiated claims that the syndrome had been recognized much earlier,[9–11] retrospective autopsy reviews suggest that the syndrome did not appear until the 1950s.[5] This fact is especially important in light of the purported association between aspirin ingestion and the development of RS, since aspirin has been in wide general use throughout the century. The sudden appearance of the syndrome suggests either an alteration in host receptivity or a new causative agent.

We previously reported a lack of association of RS

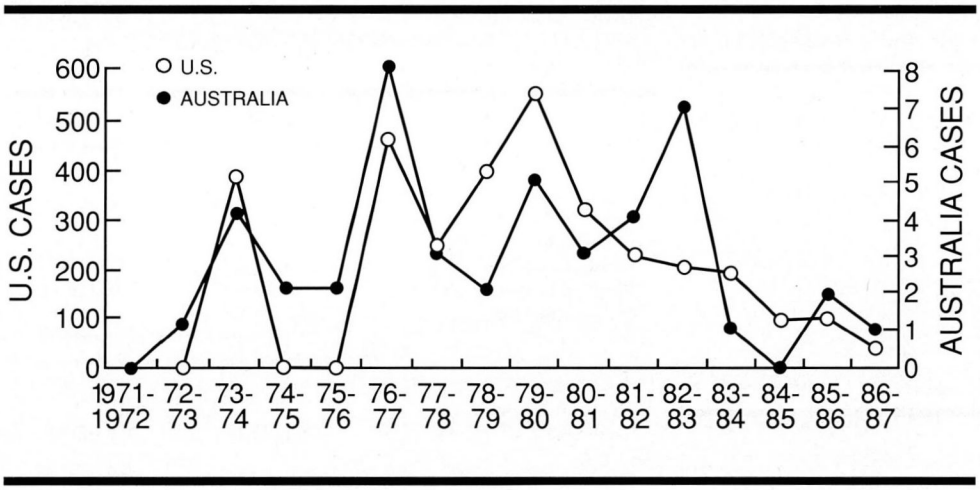

FIGURE 2. Comparison between Australia and the United States in pattern of distribution of RS cases, by year.

with salicylate ingestion in Australia, using national pharmaceutical sales data for comparison.[1] The present retrospective, case control study from Australia confirms the lack of association.

One reason for choosing Australia for these studies (besides the historical significance that RS was first described and reported from Australia) is that, as pointed out by Starko and associates in their original paper, the association between salicylate use and RS "would be easier to demonstrate in areas where salicylate use is less frequent than in the United States."[12] Our previous study demonstrated that salicylate use in Australia is very low, especially in children.[1]

Recent studies from around the world have also failed to find the overwhelming association of RS with aspirin ingestion that has characterized all of the US Public Health Service studies.[12–16] A study from South Africa[17] reported a history of salicylate administration in only 5 of 21 cases (27%), whereas a study in Ireland[18] found that 14 of 23 patients (61%) had taken salicylates. A study from Japan[19] found a 23% incidence of salicylate intake in RS cases compared with 17% in controls; in this same report,[19] 52 of 73 RS patients (71%) in Bangkok, Thailand had taken salicylates. A cooperative study by the Pediatric Intensive Care Section of the Spanish Pediatric Association[10] found only 23 of 57 (40%) of their RS patients had ingested aspirin, while a report from West Germany[21] found only 3 of 15 patients (20%) had been treated with aspirin before the onset of the disease. In Hong Kong, only 11% of cases between 1979 and 1985 received salicylates.[22] Even the long-awaited study from Great Britain[23] reported that only 59% of their RS patients had been exposed to aspirin.

Studies reporting a lack of association of aspirin ingestion with the development of RS are not limited to outside of North America. In a study from the Mayo Clinic,[24] only 20% of RS patients had taken aspirin, and the study by Lichtenstein and colleagues[6] in Cincinnati, Ohio found that fewer than half of their patients had ingested salicylates.

A report by Hall and colleagues in *Archives of Disease in Childhood*[23] was titled a "Controversy" by the journal. In an accompanying editorial commentary, Mowat[25] cautioned that we still have much to learn about RS and reemphasized some of the points Hall and associates[23] made in their study; ie, 40% of RS cases in the study had not taken aspirin and 80% of those who took aspirin had taken it in the past without ill effects. Mowat stresses the authors' own conclusion that "if aspirin has an aetiological role, there must be an exceptional, unpredictable combination of circumstances that acts as a trigger."[25]

Differential diagnoses

In both our studies, a high percentage of cases had pathologic confirmation of the diagnosis of RS—86% in this study and 90% in the previous study.[1] These figures contrast with fewer than 33% of the cases in the state or US Public Health Service studies.[12–16] Pathologic confirmation of the diagnosis of RS is critically important since so many other diseases can clinically mimic RS,[25,26] including inborn errors of metabolism.[26] Amino acid chromatography was performed in 22 of our cases and did not indicate a genetic metabolic disorder in any case.

The other medications ingested by more than one RS patient are of note because most of the liquid preparations contain alcohol, propylene glycol, sodium benzoate, and/or benzoic acid as "inactive ingredients," all of which are known to be potentially hepatotoxic and neurotoxic.

The viruses recovered from RS patients in Australia were most notable for the lack of influenza A and B

viruses. The occasional varicella-zoster virus association was seen, but the only paramyxoviruses recovered were parainfluenza and respiratory syncytial viruses. In contrast, most cases in the United States were linked to influenza A and B by temporal and geographic associations, especially during influenza outbreaks, and not by viral cultures or titers. Actual isolations of influenza A and B from patients with RS are uncommon,[5,27–29] and even serologic demonstrations of recent infection with these viruses in RS cases are rare.[30] Similar attempts to identify associated viruses in Great Britain[4] found only one influenza B and two influenza A virus (one dual virus) infections in 57 patients with RS. Also, five of our cases had evidence of a dual virus infection, compared with one control. Dual virus infections have previously been reported in association with RS,[4,31–33] and their significance may not have been fully recognized or pursued.

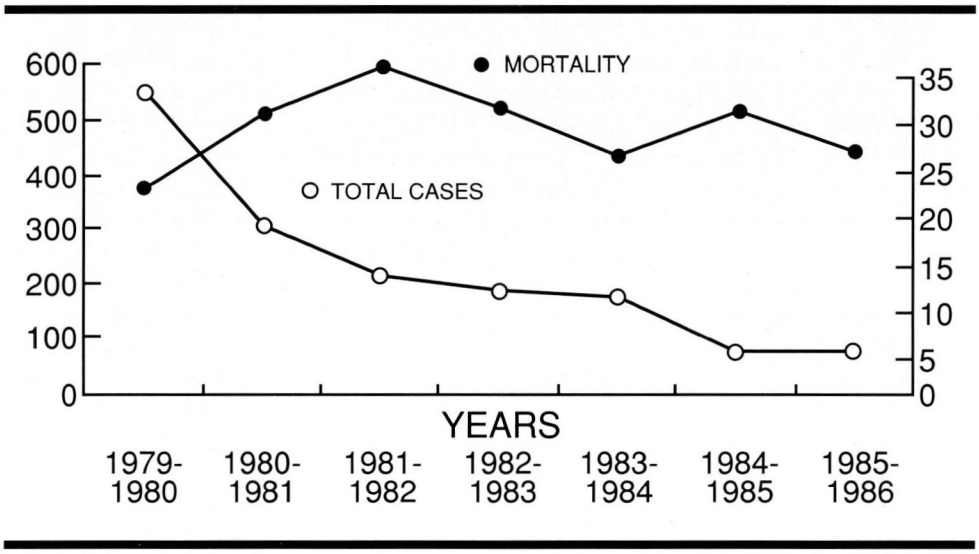

FIGURE 3. Total number of RS cases and the percent mortality in the United States from 1979 to 1986.

Age and distribution patterns

The age distribution of the Australian cases was distinctly different from that of cases in the United States,[5] but was amazingly similar to the age distribution of cases in Britain.[4]

The similar pattern of cases of RS per year between Australia and the United States (*Figure 2*) appears more than coincidental, especially in light of the lack of association of RS cases in Australia with aspirin ingestion or influenza A or B infections. The incidence of RS in Australia is similar to that of the United States, with 5 to 6 cases per million children per year. The mortality rate remains high in Australia (47%), similar to the mortality rates throughout the rest of the world (approximately 50%)[18–23] and to that of the United States as a whole (approximately 33%);[2] however, it is distinctly different from the low mortality rates (5% and 11%) reported in the recent US Public Health Service studies.[14,16]

Declining incidence or wrong diagnosis?

RS appears to be disappearing in Australia, just as it is in the United States, despite a lack of association with aspirin use. The number of cases of RS in Australia has declined dramatically since 1982. Although it is possible that a change in exposure to a toxin or a mutation in an associated virus or viruses was responsible for the sudden appearance and now the equally sudden disappearance of the syndrome, the pattern seems more consistent with an inborn error of metabolism. RS is a very rare syndrome, affecting 10 or fewer children out of every million. Viral illnesses are known to trigger the clinical expression of various genetic metabolic diseases.[26] The disappearance of RS may not be a true decrease in incidence, but rather a change in diagnostic category, so that cases previously identified as RS are now being recognized and diagnosed as inborn errors of metabolism. One such metabolic disease is medium-chain acyl-CoA dehydrogenase deficiency,[26,34,35] although the list of metabolic diseases that can mimic RS clinically and pathologically is extensive. A recent abstract suggests that 75% of cases previously diagnosed as RS would not be categorized as RS on repeat analysis, especially in light of recently described metabolic disorders.[36]

Some authors[37,38] have claimed that the decline in cases of RS in the United States lends further support to an association between aspirin and RS, because the association was brought to the public's attention and warning labels were placed on salicylates. However, careful examination of the data (*Figure 3*) reveals that the decline in RS cases in the United States began 2 to 3 years

before the Ohio study was published, and more than 5 years before warning labels were instituted.

Determination of medication use by retrospective review of medical records has been criticized as less reliable than parental interviews.[39,40] Our experience does not support this criticism. The medication histories were very thorough in the Australian medical records, and they may actually be more accurate than interview histories. Recent studies[40,41] suggest that histories are not reproducible, with interviewees changing answers based on what they believe the interviewer wants to hear and on verbal and nonverbal cues from the interviewer. As such, the second and later interviews may be totally different from the first, and the information obtained in the admission history may be more accurate than later, more directed questions.

Further evidence for the multifactorial nature of RS comes from a recent report from Italy. Andreoli and associates[42] reported on HLA-identical twins who had clinically identical upper respiratory illnesses and were treated with the same dosage of aspirin. One developed RS as diagnosed by CDC criteria, but the other did not.

CONCLUSIONS

The present case control study substantiates our previous findings of a lack of association of aspirin ingestion with the development of RS, with 42 of the 49 cases confirmed as RS by pathologic criteria. The incidence of RS in Australia has dramatically declined since 1982, despite a lack of association of RS with aspirin use.

A different burden of proof is required if one attempts to prove a hypothesis than if one wants to disprove the proposal. This is best understood with a simple analogy. If one observes 10 swans that are all white, one might propose that all swans are white. If one then observes one thousand swans and they are all white, one might hypothesize with a high degree of statistical certainty ($P<.001$) that all swans are white. But only one black swan is needed to prove that all swans are not white.[42] This study and its predecessor[1] are the black swans which prove that aspirin does not cause RS.

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