Long-term consequences of Reye syndrome: A sibling-matched, controlled study of neurologic, cognitive, academic, and psychiatric function

Sixteen survivors of Reye syndrome treated at Yale–New Haven Hospital between January, 1977, and December, 1978, received neurologic, neuromaturational, cognitive, educational, and psychiatric assessments; 12 had siblings who were also evaluated. In the RS cohort, 13 of 16 patients were in stage 3/5 coma and intracranial pressure was monitored in 12 of 16 for 4.7 days. Blood ammonia concentration was > 300 μg/ml in 13 of 16 patients with a mean peak 438. Abnormalities on neurologic examination were noted in eight RS children and in none of the siblings. No significant differences emerged on psychometric testing of RS with siblings (12 children) or on group differences (16 RS children as a group compared to 12 siblings as controls). A significant difference was noted for those four children with onset of RS under age 7 years compared to their siblings (IQ 108 vs 134). The sibling IQ-RS IQ difference was significantly correlated with age of onset of RS. Individual Full Scale IQ scores and the sibling–RS IQ differences were also correlated with severity of RS. Similar findings were observed for educational testing. Eleven of the RS children received a psychiatric diagnosis (attention deficit disorder or anxiety reaction) compared to two of the control children. Five of the RS children had experienced a significant recent life stress. As a group, children with RS remain remarkably intact; however, those with most severe RS or who were very young when affected may have some sequelae.

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THE EVENTUAL OUTCOME of survivors of Reye syndrome remains ill defined. In early studies, when an overall mortality of 32% (60% in children with most severe manifestations of the illness) was evident,[1] outcome in the survivors was considered favorable and supported the notion that RS either resulted in death or relatively complete recovery.

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Careful examinations of the survivors, however, now suggest a less sanguine picture. Davidson et al[2] noted significant psychologic deficits in seven of 11 patients (64%) and significant neurologic sequelae in 6 of 11 (54%) of survivors of RS observed over a seven-year period. Children with onset of RS when less than one year of age tended to do poorly, whereas older children appeared to be normal. Brunner et al[3] examined 40 survivors of RS over an eight-year period, and noted significant correla-

Abbreviations used

RS:	Reye syndrome
IQ:	intelligence quotent
FSIQ:	full scale IQ
ICP:	intracranial pressure
CT:	computed tomography
EEG:	electroencephalogram

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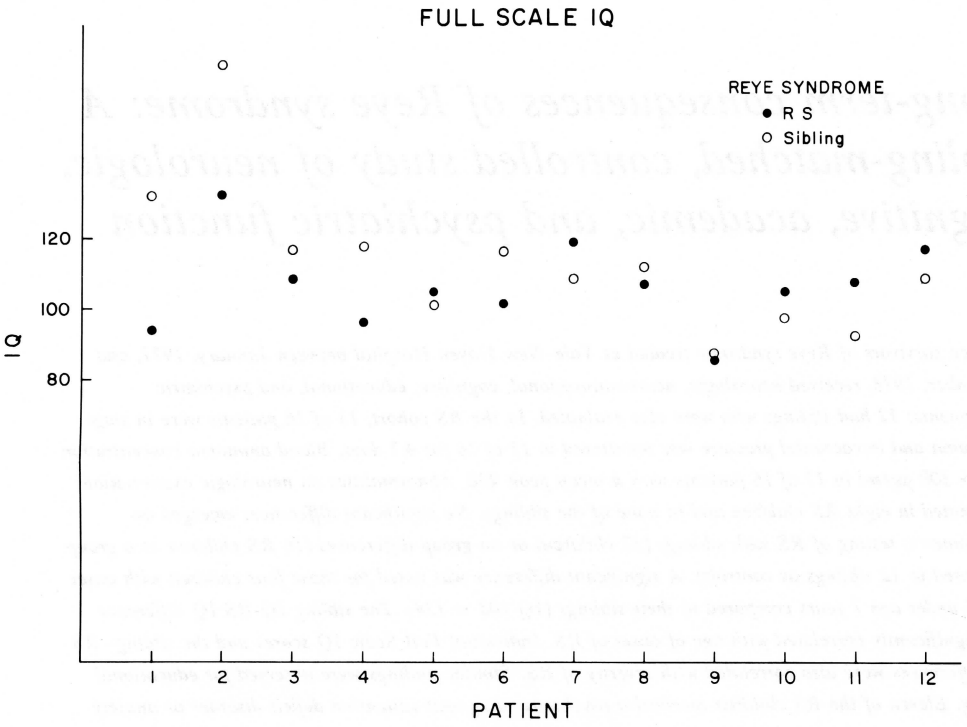

Fig. 1. Comparison of FS IQ in 12 children with Reye syndrome with their closest age-matched sibling.

tions between severity of RS (as determined by the duration of unconsciousness or the number of exchange transfusions) and deficits on intellectual, academic, and graphomotor tests. Neither the Davidson or the Brunner studies, however, incorporated an appropriate control group. Furthermore, each of the studies utilized children treated over a period of many years; thus, the treatment regimen was less likely to represent a uniform management protocol.

In order to better define some of these issues, we investigated all survivors of RS observed during a two-year period and compared their outcome with that in a matched sibling.

METHODS

Patient population. This cohort is comprised of all survivors of RS treated at the Yale-New Haven Hospital between January, 1977, and December, 1978, a period representing a time when we had accumulated significant experience with a treatment protocol that was considered standardized. A diagnosis of RS was considered on the basis of a history of persistent vomiting and progressive deterioration in the state of consciousness without focal neurologic findings. Laboratory findings of elevations in SGOT, prothrombin time, and blood ammonia concentration confirmed the diagnosis. Children were admitted to the pediatric intensive care unit and managed with intensive supportive care, including intracranial pressure monitoring if clinical status deteriorated to stage 3 coma and if the blood ammonia concentration exceeded 300 μg/ml. This treatment protocol has been described in previous publications.[1-6]

Survivors had been followed in our pediatric neurology clinic from the time of discharge, and all accepted our invitation to participate in the study. Informed consent was obtained from the parents and children, and the experimental protocol was approved by the Yale University School of Medicine Human Investigation Committee.

Survivors and their closest age-matched siblings were admitted to the Children's Clinical Research Center. During the first day, educational testing was performed and the children were fed a special diet (low catecholamines, no sugar, no additives or preservatives, salicylate-free, low monoamine oxidase inhibitors) for collection of a 24-hour urine specimen for psychopharmacologic studies. Psychometric, neuromaturational, and neurologic testing was performed during the second day. Psychopharmacologic and neuroendocrine studies, CT scan, EEG, and somatic evoked responses were performed on the third day.

The educational battery (Woodcock-Johnson) was comprised of items designed to assess reading (including word identification, word attack, and comprehension),

mathematics (including calculations and problem solving), written language (including writing to dictation and proofing), and knowledge (including science, social studies, and humanities). Graphomotor skills were assessed via the Bender Visual-Motor Gestalt test. Psychometric testing involved either the Wechsler Intelligence Scale for Children–Revised or the Stanford-Binet. The oldest sibling was tested with the Wechsler Adult Intelligent Scale.

The neuromaturational index (Yale Neuromaturational Assessment Schedule) was administered to all children and siblings except for the two youngest. It comprises measures of gross motor maturation, fine motor coordination, memory tasks, writing tasks, and measures of academic processing.[7] Psychiatric examination consisted of a clinical interview and the completion of the National Institute of Mental Health Children's Psychiatric Rating Scale[8] immediately after the interview. In addition, the parents all completed an 846 item Children's Personal Data Inventory, focusing on disorders of attention and conduct.[7] Each child was carefully examined for minor congenital anomalies (Yale Stigmata Scale[7]), and a routine neurologic examination was performed and coded immediately after the neuromaturational examination. Prior educational testing (usually group-type achievement tests, though in one case, individual achievement and intelligence testing) was available on ten children from a period preceding their illness.

Data were analyzed utilizing both parametric (linear correlation coefficients, t test, ANOVA) and nonparametric methods (Spearman rho, Wilcoxon signed rank test, sign test).[9]

RESULTS

Patient cohort. During the two-year period 18 children with RS were admitted. Of these, one girl died during admission, and one girl left the hospital in a chronic vegetative state and is not included in the analysis. Another child also had severe sequelae, but was testable and is included. Of the 16 children with RS, 12 had siblings; their data were analyzed using paired analysis. Four patients had no siblings; their data were analyzed along with the 12 utilizing group procedures (RS vs controls). Two children were too young to test utilizing the standardized educational or neuromaturational procedures.

At the time of their illness the children ranged in age from 2.8 to 14.3 years (8.9 ± 1.0, mean ± SEM), and at the time of follow-up their average age was 10.8 ± 0.86. Siblings averaged 13.3 ± 1.8 years at the time of follow-up examination, and did not differ significantly in age from the RS subjects (t = 1.34, $P < 0.05$). Overall, we

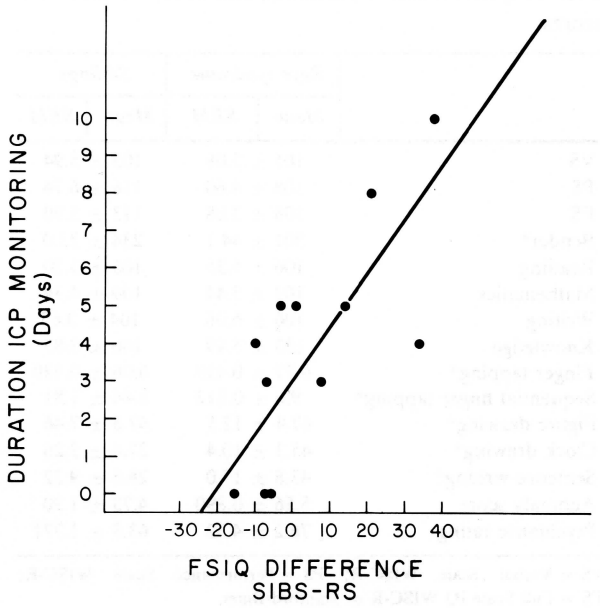

Fig. 2. Relationship between the duration of ICP monitoring in days in a child with Reye syndrome and the difference in FSIQ between that child and the closest aged-matched control. r = 0.78, $P < 0.01$.

examined ten boys and six girls with RS, but in the paired group there were seven boys and five girls compared to three boys and nine girls in the sibling group. These sex differences were not significant (chi square = 2.74, $P < 0.1$) in the paired group though they were significant in the RS vs sibling controls taking all children with RS as a group (chi square = 3.88, $P < 0.05$).

Severity of RS. Severity of RS was assessed by the initial stage of coma, duration of ICP monitoring, peak blood ammonia concentration, number of doses of mannitol during the hospitalization, and the duration of hospitalization. Thus, 13 of 16 patients were in stage 3/5 coma during the initial hospitalization, and intracranial pressure was monitored in 12 of 16 for a duration of 4.7 ± 1.1 days (mean ± SEM). Once a patient reached stage 3 coma, the trachea was intubated and the patient was monitored and maintained on a regimen incorporating controlled ventilation and phenobarbital for the duration of ICP monitoring. Thus, since the length of coma was imposed by this protocol, duration of ICP monitoring rather then duration of coma appears to be a more appropriate index of severity in this population. Blood ammonia concentration was above 300 μg/ml in 13 of 16 patients, with a mean peak 438 ± 37.1, and 11 of 16 received at least one dose of mannitol (6.3 ± 2.9) over a hospitalization that averaged 15.3 ± 3.6 days (mean ± SEM).

Neurologic abnormalities. Abnormalities on neurologic

Table. Psychometric, educational, and neuromaturational scores

	Reye syndrome		*Siblings*	
	Mean	*SEM*	*Mean*	*SEM*
VS	105 ± 3.08		103 ± 5.94	
PS	108 ± 4.60		116 ± 6.74	
FS	108 ± 3.08		113 ± 5.90	
Bender*	301 ± 44.1		234 ± 25.0	
Reading	106 ± 5.35		106 ± 3.50	
Mathematics	103 ± 5.44		109 ± 4.34	
Writing	106 ± 6.06		104 ± 3.65	
Knowledge	103 ± 5.89		106 ± 3.85	
Finger tapping*	6.27 ± 0.419		6.06 ± 0.420	
Sequential finger tapping*	9.0 ± 0.812		8.44 ± 1.81	
Figure drawing*	67.4 ± 12.5		47.6 ± 7.46	
Clock drawing*	45.3 ± 10.4		27.6 ± 3.26	
Sentence writing*	43.8 ± 17.0		28.6 ± 9.22	
Anomaly score	5.56 ± 0.890		4.73 ± 1.30	
Psychiatric rating	76.2 ± 4.32		63.3 ± 1.77†	

VS = Verbal Scale WISC-R; PS = Performance Scale WISC-R; FS = Full Scale IQ WISC-R or Stanford-Binet.
*Score represents time in seconds.
†There are no significant differences between RS and siblings except for $P < 0.05$.

examination were noted in eight children with RS and in none of the siblings. These included grimacing and apraxia in one child (transient), hyperreflexia in four (transient in all), hyporeflexia in one, a transient right hemiparesis in one child, and drooling and tics in another. Computed tomograms were normal in 15 patients and showed a moderately dilated ventricular system in one, the child with the most profound sequelae. Electroencephalograms were normal in four, probably normal or equivocal (questionable sharp activity) in 6, and abnormal in six (sharp and slow, mild generalized slowing). CT scans and EEGs were not considered to be justified in siblings.

Psychometric testing. No significant differences emerged on either paired testing of RS with siblings (12 children) or on group differences (16 RS children as a group compared to 12 siblings as controls, Table). Five RS children had higher scores than their siblings, six had lower scores, and in one pair the IQ's were almost identical (Fig. 1). No significant differences were noted between RS and siblings for any of the ten subtests.

Despite this apparent similarity between RS and siblings overall, a significant difference was observed for those four children with onset of RS under the age of 7 years when compared to their siblings (108 ± 10.4 vs 134 ± 14.2, t = 3.66, df 3, $P < 0.05$). Furthermore, the sibling IQ–RS IQ difference was significantly correlated with the age of onset of RS (r = −0.78, $P < 0.01$).

Individual Full Scale IQ scores were also significantly correlated with severity of RS. The sibling–RS IQ difference was correlated with the duration of ICP monitoring (Fig. 2; r = 0.78, $P < 0.01$; Spearmans rho = 0.72, $P < 0.02$), doses of mannitol (r = 0.65, $P < 0.05$, rho = 0.60, $P < 0.06$) and duration of hospitalization (r = 0.69, $P < 0.02$, rho = 0.77, $P < 0.03$).

Educational testing. Overall there were no significant differences between the mean scores on the Woodcock-Johnson achievement test in the RS group compared to their siblings, or on any of the subtests, using either paired testing (n = 12) or group testing (16 RS vs controls, Table). However, as with psychometric test results, significant correlations were apparent between severity of the illness as measured by duration of ICP monitoring, doses of mannitol, or days in the hospital and many of the educational subtest scores.

Achievement test results are available both before and after illness for ten children with RS; of these ten, nine had siblings available for comparison. Six of nine either had no change from their pre-RS level or actually improved their performance. Two of those children with a demonstrable decline in achievement testing, declined predominantly because of a decrement in mathematics scores. The scores of the third child fell in all areas, but he had been known to have significant academic problems beforehand, and though his results were low, his sibling was also impaired.

Neuromaturational testing. Results on such items as figure drawing, clock drawing, timed writing, finger tapping (both thumb-index and sequential finger tapping), and Bender figure drawing indicated no significant differences between RS and controls, although in each timed task there was a trend for RS to perform more slowly than control children (Table). Significant correlations were observed, however, between some of the neuromaturational items and measures of severity (e.g., duration of ICP monitoring–Bender times; doses of mannitol–Bender times; duration of hospitalization–Bender times) and between items on this scale with each other (sequential finger tapping–finger tapping).

Significant differences were noted on the face-hand extinction test (chi square = 6.24, $P < 0.025$) and in the visual memory object span test (chi square = 4.91, $P < 0.05$) between RS and controls. Analysis of differences on the other items on this test, including gross motor and fine motor development, finger agnosia, right-left discrimination, and academic processing, failed to demonstrate differences between RS and controls (chi-square analysis).

Psychiatric evaluation. Eleven of the RS children received a psychiatric diagnosis compared to only two of the control children (chi square = 7.8, $P < 0.01$). These

diagnoses were primarily of two types: an attention deficit disorder with hyperactivity or an anxiety reaction that seemed to have been generated by the illness. In eight of 11 patients the psychiatric diagnosis appeared to follow the acute illness; those three patients in which it was not clearly related to the illness were children who were depressed over marital discord or divorce. In children with RS the psychiatric rating obtained on the NIMH Children's Psychiatric Rating Scale was significantly different compared to controls (Table) and was also correlated with severity of RS as determined by the doses of mannitol administered.

The pattern of behavior following RS was quite stereotyped for all children interviewed. During the initial six-month period after the illness the child was irritable; the words "cry baby" were used frequently by the parents to describe their affected youngsters. During this time the children were also distractable, agitated, inattentive, impulsive, and quite fidgety and active. The family would try to be very gentle with the child and the parents often described everybody as "walking on eggs" in order to minimize upsetting the child.

In two cases a rather rapid return to normal after the first six months was described, but in the remaining children, the next 18 months after illness were characterized by gradual improvement but not complete return to normal. Only two children were considered by their parents to be totally back to normal; the rest considered their child to have some deficit.

The psychiatric consequences of such a life-threatening illness is one child in the family were evident in the parents' perception of their ill child and on the family unit itself. A frequently observed phenomenon was increased anxiety whenever the RS child had a minor illness. Furthermore, at least during the acute stages, underlying personality traits tended to become accentuated. Previous speech problems and learning problems were perceived as intensified in several children, and the effects of RS on academic performance were always of great concern. In a number of cases the siblings became jealous of the RS child, though in four of the families the parents believed the acute illness had a positive effect by bringing the family members closer together. In others, the illness was thought not to affect the family at all. In two cases, parental divorce was related to the illness, but this had been expected based on the degree of marital discord which preceded RS, so that the acute illness appeared to represent only a precipitating factor bringing a long, shaky marriage to dissolution.

In five children a significant life stress preceded RS by approximately one month. In one child this life stress was represented by a major move from one locale to another. In the remaining four, the stress was the result of parental divorce, either contemplated or during the stage of being completed at the time when they developed RS.

DISCUSSION

We have attempted to circumvent some of the methodologic difficulties that have limited the interpretation of previous studies of the long-term consequences of RS. Of these, perhaps the most significant involves the failure to include an adequate control group, without which it is difficult to decide whether abnormalities uncovered on psychometric and educational testing are the result of RS or would have appeared de novo. Conversely, if children who recover perform in the "normal" range, one might speculate that had they not had RS, their performance on psychoeducational testing might have been considerably higher. Furthermore, a sibling-matched control group should lessen the possibility of what Brunner et al[3] termed "modulator variables" (such as socioeconomic status) influencing potential differences between RS and controls.

Evidence from a number of studies, reviewed by Erlenmeyer-Kimling and Jarvis,[10] indicates a close relationship between the FSIQ scores of siblings reared together. We found a correlation of 0.83 ($P < 0.001$) for sibling-sibling FSIQ, indicating that the same general relationship was apparent between RS children and their unaffected siblings as is found between two normal siblings.

Another limitation of earlier investigations was the utilization of patients who had RS over periods as long as eight years. Such a long duration is fraught with difficulties, including changes in the physician sensitivity to the diagnosis, the availability of diagnostic tests, and change of treatment regimens. By limiting our cohort to children diagnosed and treated within a two-year period, we hoped to minimize the potential variability and modifications in patient management that might influence long-term outcome.

However, despite this relatively sanguine picture, a number of findings suggest that the more severe the encephalopathy, the more severe the deficits, particularly in the most immature brains, a finding not immediately apparent from simply observing RS patients as a group compared to siblings. Because newer management techniques have been so successful, it is no longer appropriate to utilize mortality as the principal criterion of severity; correlations with outcome must depend upon more subtle determinants of clinical state. Among these, intracranial pressure is perhaps the most important factor. Our results indicate that children with severe RS, as measured by the difficulty in controlling ICP (number of doses mannitol

required) and the duration of increased ICP (duration of ICP monitoring) as well as an overall index of severity (duration of hospitalization) are more likely to have lower FSIQ than their unaffected siblings.

Previous studies have differed on the relationship between age at the onset of RS and subsequent neuropsychiatric or educational sequelae. Davidson et al[2] noted IQ's less than 25 in three of four children with onset of RS under age one year, and an average IQ of 73 in four children with onset between one and three years, but IQ in three children with onset beyond three years averaged 120. Brunner te al[3] found a negative correlation between age of onset and performance on tests of concept formation and abstract thinking, indicating that children who developed RS later in life tended to do poorly in this task. We found a significantly lower mean FSIQ for four children who developed RS before age 7 years compared to their siblings. Furthermore, we observed a significant negative correlation between the age of onset of RS and the FSIQ difference between siblings and RS patients; the greater the difference between the sibling control and the RS child's FSIQ, the younger the age of onset. Thus, in addition to the relationship between severity and sequelae noted earlier, our findings also suggest a relationship between age at the time of RS and the emergence of subsequent difficulties.

Of particular interest to us was the unusually large number of children who had experienced a significant life stress within one month prior to the development of RS. Abundant evidence indicates a relationship between life stress and the development of a variety of psychiatric disorders,[11] but our findings also suggest a possible relationship between life stress and the development of an acute encephalopathy. Explanations for this unexpected finding could involve the interactions of many neural systems, but we would speculate that brain monoaminergic systems play an important role in this process. A number of investigations indicate abnormalities in brain monoamines,[12] their precursor amino acids,[13] or their metabolites in RS.[14] Evidence from several lines of investigation suggests a role for brain monoamines in life stress.[15] We speculate that this commonality in both life stress and RS indicates that brain monoaminergic mechanisms may play a role in the pathogenesis of this disorder, and should stimulate more studies designed to explore these issues in greater detail.

Our results suggest that those with most severe RS, as evidenced by the degree and duration of increased ICP and those very young when affected, may have some sequelae. However, as a group children with RS remain remarkably intact, and our investigation serves to reassure those caring for children with RS that their intense therapeutic efforts will be rewarded not only with survival, but with recovery without significant loss in academic achievement or intellectual functioning.

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