Neuropsychologic consequences of Reye syndrome

Behavioral measurement of brain function was conducted in 40 children, one or more years after their recovery from Reye syndrome. Test measures included standard indices of intelligence, school achievement, visual-motor coordination and social maturity, plus the Halstead-Reitan Neuropsychological Batteries. There was a strong correlation between the degree of impaired neuropsychologic function and clinical grade at admission, the duration of impaired consciousness, and the number of exchange transfusions required. Patients with milder disease had normal brain function and fewer school problems. Language and perceptual-motor performance significantly improved with increasing years in recovery, suggesting that some of the disturbances of brain functioning are transient. The statistical analysis indicated that there are lasting, often subtle disturbances of higher cognitive function as a result of Reye syndrome. These deficits, not always apparent on clinical examination, are clearly correlated with the extent of neurologic involvement. This quantitative assessment of neuropsychologic function is a basis for determining the "quality of survival" in Reye syndrome, and such measurements should be included in the comparative evaluation of Reye syndrome treatment programs.

Robert L. Brunner, Ph.D.,* Donald J. O'Grady, Ph.D.,
John C. Partin, M.D., Jacqueline S. Partin, M.S., and
William K. Schubert, M.D., *Cincinnati, Ohio*

CURRENTLY, more than half of all patients with Reye syndrome recognized in the United States progress to coma, with wide variations in subsequent mortality and morbidity, depending on geographic region and the institution in which they were treated. The average mortality is 40%, and 10% of the survivors are left severely brain damaged.[1] Special treatment centers, however, report mortalities of 20% or less,[2, 3] perhaps due to earlier and more reliable diagnosis. Moreover, intensive care given may help control the increased intracranial pressure which is often a fatal consequence of the disease.

The status of children surviving after coma in Reye syndrome has not been fully investigated using quantitative psychologic and neuropsychologic test measures. One of the few reports is that of Davidson and coworkers,[4] who compared the psychologic and neurologic status of 11 children who had Reye syndrome with that of survivors of other diseases of the central nervous system. Those with Reye syndrome had a wide range of disabilities, including disturbances in language, measured intelligence, and social maturity[3, 4] similar to those found following other encephalopathies. Davidson found that surviving older children tended to be less handicapped than younger children, but his sample was small, only three of the 11 patients being over 3 years of age.

Abbreviations used
WRAT: Wide Range Achievement Test
SES: socioeconomic status

The purpose of the present study was to obtain quantitative information on residual neuropsychologic disability in children who had had Reye syndrome, following use of a standard diagnostic and treatment program. The data should provide a basis for the comparison of the outcomes of various treatment systems.

From the Institute for Developmental Research of the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

Supported by Project 427, Maternal and Child Health Services, Mental Health and Health Services Administration, Grant RR00123, from the National Institutes of Health, United States Public Health Service.

Reprint address: Children's Hospital Research Foundation, Elland and Bethesda Aves. Cincinnati, OH 45229.

0022-3476/79/110706+06$00.60/0

SUBJECTS

The subjects of this study were 40 children (15 males, 25 females) who had Reye syndrome, confirmed by liver biopsy, one to 7 years prior to participation in the study. The children were among 66 survivors of Reye syndrome who had been treated at the Cincinnati Children's Hospital between 1969 and 1977 and followed continuously after discharge in a special clinic. Parents of these 40 children had accepted a written request to become involved in the study.

ILLNESS CLASSIFICATION VARIABLES

Earlier reports provided details of clinical symptoms,[3] morphology,[7-9] and treatment[10] in the cases of Reye syndrome treated at the hospital from which the present sample was taken. Electron microscopic examination of liver biopsy, usually done within two hours of admission, was used in all patients in the present study to confirm the diagnosis.[7]

Estimation of severity of CNS involvement was made at the time of admission (Table I). A clinical grade was assigned to each patient based on the state of consciousness, respiratory pattern, pulse characteristics, state of retinal vessels and optic discs, and the responsivity of the pupils and the skeletal musculature. Numerical grades of severity 1 and 2 represented mild-to-moderate neurologic involvement. Grade 3 represented coma with moderate decerebrate state; grade 4 represented coma with severe neurologic signs; and grade 5 was tantamount to "brain death" with evolving decorticate state.

An estimate was made of the number of hours of imparied consciousness by reviewing the medical charts for several endpoints. On admission parents were asked to recall the date and time when the child first became combative, failed to recognize his parents, or, in the case of infants, appeared unconscious. Any one of these criteria indicated the onset of impaired consciousness; its termination was the point when the infant returned to consciousness or the child became coherent in response to questioning, was no longer combative, and began to ask for and recognize his parents.

The length of time between the onset of the vomiting and the diagnosis of Reye syndrome by liver biopsy was computed.

A description of the method of treatment of Reye syndrome at Children's Hospital has been published elsewhere.[11] It includes supportive measures and repeated exchange transfusion in the event of rapidly declining neurologic status or frank coma (that is, grade 2 with rapidly progressing disease, and grades 3 and 4). Transfusions were not administered prophylactically. After admission, a period of eight to ten hours elapsed prior to the first blood exchange. A second transfusion, if required, followed the first by eight hours. Subsequent transfusions were given 12 hours apart. Mean values for number of transfusions and clinical grade are displayed in Table II.

Table I. Clinical grades of Reye syndrome at admission

Clinical grade	*Symptoms*
Mild-moderate	
1	Unusually quiet, lethargic, without other neurologic findings
2	Lethargic, slurred speech; motor movements gross; normal pupils, slight distention of retinal veins; brief periods of loss of contact
Severe	
3	Coma lasting less than 3 hours; intermittent seizures and agitation; plantar sign positive; pupillary size normal to dilated; light response normal; fundal veins dilated
4	Protracted coma, seizures, agitated and combative; decerebrate posturing; plantar sign strongly positive; tachycardia, tachypnea; pupillary response sluggish to strong light; fundal veins engorged, discs blurred
5	Fixed dilated pupils; respiratory arrest; decerebrate posturing changes to paralysis

Table II. Illness/modulator variables: Descriptive data for independent variables

Variables	*No. of patients*	*Mean*	*Standard deviation*	*Range*
Age at onset (mo)	40	84.6	46.4	4-180
Years post recovery	40	2.7	1.7	1-8
Number of transfusions	40	1.8	2.4	0.9
Clinical grade	40	2.9	1.2	1-4.5
Hours of altered consciousness	37	56.2	97.5	0-504
Hours between vomiting and biopsy	37	54.9	29.4	24-144
Socioeconomic status	38	3.5	0.9	1-5

NEUROPSYCHOLOGIC VARIABLES

Overall psychometric intelligence was assessed in 40 post-Reye syndrome subjects utilizing either the Stanford-Binet (n = 2) or the Revised Wechsler Intelligence Scale for Children (n = 37). One child, less than 2 years of age during the study, was assessed with the Bayley Scales of Infant Development. Only the Wechsler scores were analyzed. Among these, two scores fell below tabled

Table III. Psychologic variables: Descriptive data (standard scores) for dependent psychologic measures

Variables	No. of patients	Mean	Standard deviation
Full scale IQ	35	98.6	19.8
Verbal IQ	35	95.2	18.5
Performance IQ	35	100.3	18.3
Reading	35	99.7	21.7
Spelling	35	97.7	24.5
Arithmetic	35	90.7	13.7
Draw-A-Person	24	83.5	15.7
Social quotient	37	102.8	18.6

norms and were not included in the statistical analysis.

School achievement was surveyed in 35 of the subjects with the Wide Range Achievement Test and its associated norms.[12] The WRAT includes subtests for evaluation of spelling, reading, and arithmetic.

Neuropsychologic status of 33 chilren was assessed using age appropriate variations of the Halstead and Reitan tests. These test batteries, empirically derived, differentiate between intact individuals and those with central nervous system disorders. They screen reasoning, motor speed, strength, attention, memory, language, perceptual-motor integration, lateral dominance, visual, haptic and auditory sense modalities. Twenty-one children from 9 to 14 years of age (n = 21) were given the Halstead Test Battery for Older Children. The two children over 14 were given the Halstead Neuropsychological Test Battery for Adults. The remaining seven children, who were less than 5 years of age, were not given the Halstead-Reitan Tests.

Neuropsychologic test scores for statistical evaluation were obtained by comparison of the subject's score with published norms for the appropriate age and calculation of a T score[13].*

Grapho-motor skills were evaluated by means of the Bender Visual-Motor Gestalt Test (n = 16) and Draw-A-Person (n = 24). The Bender Test was scored according to the published normative values for errors, significantly correlated with organic brain disease.[14] In addition, the number of instances of confused figure order was tabulated. The Draw-A-Person criteria and norms were obtained from Harris.[15] One or both parents participated in a structured diagnostic interview, using the Vineland Social Maturity Scale.

During the course of this study, 13 nonreferred siblings of hospital patients and volunteers were also tested as controls. Their scores were compared with those published by Klonoff and Low.[13] These control values were well within normal limits, supporting the use of the Klonoff and Low means and standard deviations as norms in evaluating scores obtained in our setting.

*The T score is a standardized distribution with a mean of 50 and a standard deviation of 10.

MODULATOR VARIABLES

Modulator variables refer to patient characteristics that were not specifically medical or psychologic, including age at onset and years postrecovery from the acute phase, as shown in Table II. Another variable, socioeconomic status of the patient's family, was ranked between 1 and 5 on the basis of established criteria[16]; these data are also shown in Table II. The gender of the subject was considered to be a modulator variable for the purposes of statistical analysis.

RESULTS*

Illness classification variables. Pearson correlation coefficients (two-tailed) were computed among the following variables: age at onset of Reye syndrome, grade of severity, hours between vomiting and biopsy, hours of altered consciousness, and number of transfusions. Statistical significance was demonstrated in only three relationships. The correlation coefficient between grade of severity and number of transfusions was significant ($r = 0.66$, $P < 0.01$). Grade of severity also was significantly related to hours of altered consciousness ($r = 0.57$, $P < 0.01$). Number of transfusions correlated with hours of altered consciousness ($r = 0.77$, $P < 0.01$) and hours between vomiting and biopsy ($r = 0.37$, $P < 0.05$).

Modulator variables. The mean socioeconomic status rating of the sample was 3.50 ± 0.9. The mean number of years postrecovery was 2.75 ± 1.73. No correlation coefficients between modulator variables and illness classification variables reached statistical significance.

Using the Student t test for differences, males and females were compared in age at onset, years in recovery, grade of severity, SES, IQ, achievement, and Halstead-Reitan measures. On none of these comparisons did the t values approach statistical significance. Thereafter, all further analyses of the data from males and females were combined.

Neuropsychologic variables. Mean standardized scores of neuropsychologic tests are presented in Tables III and IV as standard scores or T scores with the corresponding standard deviations. Not unexpectedly, considerable association was found among the different behavioral variables. More than 100 significant correlations were found;

*A supplement is available upon request from the first author which gives the results in greater statistical detail.

two were notable. Measures of intelligence (full scale, verbal, performance) were generally highly correlated with each other and with academic ability (WRAT reading, etc.). Both scholastic achievement and intelligence tended to be correlated with the Halstead-Reitan measures.

Pearson correlation coefficients were computed between illness/modulator variables, intelligence, achievement, graphomotor skill, and social maturity. The majority of significant correlations involved either the number of transfusions, hours of altered consciousness, or SES. In those requiring larger numbers of transfusions or with longer duration of altered consciousness, the intellectual, academic and graphomotor scores were lower. These correlations were signficant ($P < 0.05$) and were between $r = -0.36$ and $r = -0.60$. Age at onset correlated significantly only with arithmetic achievement ($r = -.41$; $P < 0.01$). As the age at admission of the patient increased, arithmetic scores on the WRAT tended to decline. Measured intelligence, academic achievement, and social maturity tended to be lower in children of families with lower socioeconomic status. Socioeconomic status and grapho-motor skill were not systematically associated.

Step-wise multiple regression analyses were computed in order to separate the effects of SES from the illness variables. We found 15% of the variance in IQ was due to SES. Nineteen percent of the variance in overall IQ could be explained by the effect of the number of transfusions. The remaining known variables did not make an appreciable contribution. For achievement scores, the variance was similarly apportioned.

Unlike the intellectual-academic test results, the Halstead-Reitan Neuropsychological test scores did not significantly correlate with SES. Highly significant negative correlations were found between illness variables such as the number of transfusions, hours of altered consciousness, clinical grade and the Tactual Performance Test, Category Test, and the Trail Making Test measures of the Halstead-Reitan battery. Moreover, significant positive correlations (r's = .44 to .49; $P < 0.05$), suggesting recovery or improvement, were found between years postrecovery and several measures of the Tactual Performance Test as well as the Speech Sounds Perception Test.

Age of onset and Category Test (concept formation or abstract thinking) performance were significantly negatively correlated, indicating that children who developed Reye syndrome later in life tended to do more poorly on this test of concept formation ability. This was confirmed by a step-wise multiple regression analysis, which indicated that 33% of the variance in Category Test scores was accounted for by the age at the onset of the disease.

Table IV. Neuropsychologic variables: Descriptive data (T scores) for dependent neuropsychologic measures

Variables	*Cases*	*Mean*	*Standard deviation*
Color form (time)	8	50.9	14.9
Color form (errors)	8	45.9	12.2
Matching V's (time)	8	52.3	8.8
Matching V's (error)	8	53.0	9.9
Matching figures I	8	49.7	8.4
Matching figures II	8	55.2	2.1
Target test	8	53.9	6.0
Progressive figures	10	49.3	14.3
Speech sounds perception	23	49.7	16.9
Tactual performance test (dom.)	30	39.4	15.0
Tactual performance test (non dom.)	30	39.8	15.6
Tactual performance test (both)	30	45.2	15.5
Tactual performance test (total)	33	38.2	14.2
Tactual performance test (memory)	33	44.1	14.3
Tactual performance test (localization)	33	43.9	14.7
Category test	33	42.4	14.9
Tapping (dominant)	30	50.7	11.8
Tapping (non dominant)	30	50.2	11.9
Trail making A	20	50.4	12.3
Trail making B	20	47.2	16.2
Bender (confused order)	16	46.2	11.0
Bender (significant signs)	14	3.7*	2.8
Seashore rhythm test	22	5.9†	3.7

*Frequency of significant errors.
†Frequency of errors.

In order to provide more information about individual patients, the psychologic and neuropsychologic test results were examined by a clinical neuropsychologist who did not have knowledge of the severity of the disorder in the individual cases. Based only on the test scores, the neuropsychologist made clinical judgments about the likelihood of brain dysfunction in each child. Three classes were formed; no evidence, equivocal evidence, and clear evidence of brain-related disturbance. The average severity of illness in terms of clinical grade, transfusions, and hours of altered consciousness were then computed for each class and are presented in Table V. Only one child in the group with clear evidence of brain

Table V. Clinical neuropsychologic judgment made one or more years after Reye syndrome (n = 38)

	Clinical grade	No. of transfusions	Hours of altered consciousness
No evidence of brain dysfunction (n = 15)	2.5 (1-4)	1.1 (0-4)	21.1 (0.60)
Uncertain neuropsychologic findings (n = 10)	2.2 (1-4)	0.5 (0-2)	20.4 (0-68)
Clear evidence of brain dysfunction (n = 13)	3.7 (2-4.5)	3.5 (0-9)	129.5 (24-504)

dysfunction had a clinical grade below 3. His illness was complicated by a long vomiting-biopsy interval (six days) and evidence of salicylate toxicity. All other children in this class had clinical grades greater than 3. The parents of the children were contacted in 1978 and interviewed about their child's school performance. The 12 in the group with clear evidence of brain dysfunction were reported to have school difficulties in all cases, including grade failures and placement in special classes or schools.

In the group of children who were judged to have no evidence of brain dysfunction by test score profiles, two children had clinical grades greater than 3. The illness-test intervals were 5 and 3 years, respectively. Both are reportedly performing well in school. In one of the two, because of behavioral problems, counseling has been sought by the family from a psychologist. Of the remaining children without evidence of brain dysfunction, one had required special help in school which involved remedial reading, and another "doesn't apply herself" (according to mother), earning low average grades. Four of the children whose neuropsychologic profiles yielded uncertain evidence of brain dysfunction had educational difficulties. One had a tutor, but needed similar help before the illness. The other reports in this group included below average grades and placement in a learning disability class.

DISCUSSION

Quantitative studies are needed to determine the extent of permanent brain damage in children recovering from Reye syndrome, and to determine the quality of survival after coma and the complex regimens required for treatment. Furthermore, Reye syndrome mainly affects schoolchildren and occurs during the winter months. The patients usually return to school soon after recovery from the encephalopathy; for these children, the detection and characterization of defects of brain function, even if transitory, are needed promptly. An adequate neuropsychologic examination may reveal deficits which are not apparent from brief or more casual examination. With this assessment, proper counseling can be given, thereby mitigating school adjustment problems and attendant emotional reactions.

The results of this study support the clinical observations of an association between the severity of the encephalopathy of Reye syndrome and the behavioral outcome. In general, the length of the period of disordered brain function during the acute stage of the illness (and correspondingly the total number of exchange transfusions) was the best predictor of the eventual neuropsychologic outcome, correlating higher with eventual outcome than did clinical neurologic "grade" at time of admission.

Clinically, this study may enhance the physician's understanding of the relationship of measures of brain involvement with functional capacity, and aid in counseling parents of children recovering from Reye syndrome. The study suggests that some patients with apparently good clinical recovery may have subtle neuropsychologic defects. The Halstead-Reitan neuropsychologic tests have a proven capacity for distinguishing patients with structural brain lesions,[17] and are also helpful in measuring the impact of structural lesions on day-to-day functioning.[18] Our study shows that deficits of measured intelligence, school achievement, visual-motor integration, sequencing, tactile problem solving, and concept formation increased as a function of severity of disease. On the other hand, visual and auditory perception, social-adaptive development, and digital motor speed were not significantly associated with disease variables.

School problems occurred in 85% of children who had been comatose and who had an initial neurologic rating of 3.2 or greater. In this same group, 73% had clear neuropsychologic test deficits.

Only six children in this study classed grade 3 or lower had subsequent psychoeducational difficulties. Two were receiving low grades, two needed extra help, one failed, and one was in special class placement. However, more school-aged children must be studied before a clear picture can be gained of the impact of Reye syndrome on school performance.

It appeared that individuals who were older when they developed Reye syndrome performed more poorly in concept formation and arithmetic computations than

younger children. Younger children may have been "spared" deficits because the younger brain may be less "vulnerable" to the effects of encephalopathy or it may have more "recoverability." Neuropsychologic testing showed that no function declined and two appeared to "recover" with time: the perception of speech sounds and Tactual Performance Test scores. Both improved as more time elapsed between illness and testing. Language functioning[19] and motor ability[20] have previously been shown to improve with time after brain damage due to various causes.

Many important questions about the late results of Reye syndrome still require answers. Since the duration of coma is significantly correlated with outcome, its course should be followed at regular intervals using a system of consistent observations.[21]

REFERENCES

1. Crocker J, editor. Reye's syndrome: The proceedings of a symposium, New York, 1979, Grune & Stratton, Inc.
2. Corey L, and Rubin RJ: Reye's Syndrome 1974: An epidemiological assessment, *in* Pollack JD, editor: Reye's syndrome, New York, 1975, Grune & Stratton, Inc., pp 179-187.
3. Partin JC: Reye's syndrome (encephalopathy and fatty liver): Diagnosis and treatment, Gastroenterology 69:511, 1975.
4. Davidson PW, Willoughby RH, O'Touma LA, Swisher CN, and Benjamins D: Neurological and intellectual sequelae of Reye's syndrome: A preliminary report, *in* Pollack JD, editor: Reye's syndrome, New York, 1975, Grune & Stratton, Inc., pp 55-59.
5. Brink JD, Garrett AL, Hale WR, Woo-Sam J, and Nickel VL: Recovery of motor and intellectual function in children sustaining severe head injuries, Dev Med Child Neuro 12:565, 1970.
6. Klonoff H, Low MD, and Clark C: Head injuries in children: A prospective five year follow-up, J Neurol, Neurosurg Psychiatry 40:1211, 1977.
7. Partin JC, Partin JS, Schubert WK, et al: Brain ultrastructure in Reye's syndrome, J Neuropathol Exp Neurol 34:425, 1975.
8. Partin JC, Schubert WK, and Partin JS: Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty alteration of the viscera), N Engl J Med 185:1339, 1971.
9. Bove KE: The character and specificity of the hepatic lesion in Reye's syndrome, *in* Pollack JD, editor: Reye's syndrome, New York, 1975, Grune & Stratton, Inc., pp 93-116.
10. Bobo RC, Schubert WK, Partin JC, and Partin JS: Reye's syndrome: Treatment by exchange transfusion with special reference to the 1974 epidemic in Cincinnati, Ohio, J PEDIATR 87:881, 1975.
11. Schubert WK, Bobo RC, Partin JC, et al: Reye's syndrome, Disease-a-month, December 1-30, 1975.
12. Jastak JF, and Jastak SR: The wide range achievement test, Wilmington, 1976, Guidance Associates of Delaware, Inc.
13. Klonoff H, and Low M: Disordered brain function in young children and early adolescents: Neuropsychological and electroencephalographic correlation, *in* Reitan RM, and Davison L, editors: Clinical neuropsychology: Current status and applications, New York, 1974, Winston, Inc., pp 121-178.
14. Koppitz EM: The Bender Gestalt test for young children, New York, 1963, Grune & Stratton, Inc.
15. Harris DB: Children's drawings as measures of intellectual maturity, New York, 1963, Harcourt, Brace & World.
16. Hollingshead AB: Two factor index of social position, unpublished manuscript 1957, Yale University, New Haven, Connecticut.
17. Russell EW, Neuringer C, and Goldstein G: Assessment of brain damage: A neuropsychological key approach, New York, 1970, Wiley-Interscience.
18. Turpin EW, and Townes BD: Neuropsychological evaluation as an adjunct to behavioral interventions with children, Pro Psychol 7:153, 1976.
19. Kertesz A, and McCabe P: Recovery patterns and prognosis in aphasia, Brain 100:1, 1977.
20. Laplane D, Talnirach V, Meininger J, Bancaud J, and Orgogozo JM: Clinical consequences of corticectomies involving the supplementary motor area in man, J Neurol Sci 34:301, 1977.
21. Bates D, Caronna JJ, Carledge NEF, et al: A prospective study of non-traumatic coma: Methods and results in 310 patients, Ann Neurol 2:211, 1977.