0090-2493/82/1009-0583$02.00/0
CRITICAL CARE MEDICINE
Vol. 10, No. 9

Printed in U. S. A.

Intellectual and emotional sequelae of Reye's syndrome

PAULINE Y. BENJAMIN, PHD; MORRIS LEVINSOHN, MD; DENNIS DROTAR, PHD; ELIZABETH E. HANSON, RN

Previous reports on survivors of Reye's syndrome have indicated a high proportion of significant neurological and intellectual sequelae. However, increasingly sophisticated monitoring and therapeutic techniques have diminished both the mortality and morbidity of this disease. Our present study documented the relatively good intellectual and neurological prognosis for recent survivors of Reye's at our institution and explored the emotional impact of this illness on survivor's families.

The significant emotional problems of the children and their families were in striking contrast to the relatively good intellectual and academic recovery. Nine of the 16 survivors showed emotional disruption (primarily somatic complaints, anxiety, and depression). Fourteen of 16 mothers interviewed continued to suffer from anxiety, depression, and overprotective behavior as long as 5 years after their child's illness. In many respects, the parents endured more prolonged and profound suffering than did the children. These findings have implications for the delivery of follow-up care to families of survivors.

Advances in the diagnosis and treatment of Reye's syndrome have dramatically improved the survival rates of this life-threatening condition[1-7] and directed attention to the quality of life of survivors. Recent reports indicate varying rates of neurological and intellectual sequelae among surviving children.

Davidson et al.[8] reported a series of 11 survivors of Reye's syndrome hospitalized between 1967 and 1974, noting that only 4 children were without major intellectual and neurological sequelae. Six of 11 children had IQs below 80 and 5 had major neurological findings such as quadriplegia, hemiparesis and cortical blindness. Brunner et al.[9] studied a series of 33 children hospitalized between 1969 and 1977, and reported that 11 had evidence of brain dysfunction on neuropsychological testing and manifested impairment severe enough to warrant placement in classes for the retarded or cause grade failure at school. Another one-third had uncertain evidence of neuropsychological dysfunction; several required learning disability classes or supplemental tutoring. Shaywitz et al.[10] reported on outcome for a series of 29 children, indicating that 3 of 27 survivors were severely neurologically disabled.

From the Divisions of Pediatric Psychology and Pediatric Neurology, Department of Pediatrics, Rainbow Babies and Childrens Hospital, Case Western Reserve University, Cleveland, OH.

Address requests for reprints to: Dr. Levinsohn, Room 684A, Rainbow Babies and Childrens Hospital, 2101 Adelbert Road, Cleveland, OH 44106.

To our knowledge, no studies have systematically explored the emotional impact of Reye's syndrome. However, there is preliminary evidence that Reye's syndrome and other acute life-threatening illnesses can seriously compromise the emotional adjustment of survivors and their families. Shaywitz et al.[11] noted that 2 of 3 Reye's survivors studied manifested "emotional lability" and that the third was "withdrawn" upon hospital discharge. Benjamin[12] studied a group of children referred for psychological consultation after acute life-threatening illness. That group (which included no children with Reye's syndrome) had a high incidence of severe and longstanding emotional reactions in affected children and their parents, despite the fact that the children had made good medical recoveries.

The present study is a comprehensive, standardized assessment of the intellectual, neurological, and emotional adjustment of recent survivors of Reye's syndrome and their families.

Setting

Rainbow Babies and Childrens Hospital is a large (220-bed) primary and tertiary pediatric care center. Its ICU is a referral center for critically ill children throughout northeast Ohio. The hospital has a liberal policy with respect to patient visitation. Parents are permitted to room-in at the hospital and encouraged to visit their children in the ICU. The nature of their child's illness and the treatment protocol are discussed with parents in a quiet private setting, as soon after hospital admission as possible. Although social work and psychological consultation is available, it has not been a routine part of the care provided families of children with Reye's syndrome.

Treatment Protocol

Initial treatment consists of precise documentation of each patient's changing neurological status and intensive supportive care with correction of metabolic derangements. Exchange transfusions using an arteriovenous Scribner shunt were performed through 1977. Since 1975, continuous intraventricular pressure monitoring with polygraphic recordings of intracranial pressure, arterial blood pressure, central venous pressure, and tidal partial pressures of carbon dioxide (P_{CO_2}) has been routine. Controlled hyperventilation using pancuronium bromide paralysis is employed, and P_{CO_2} is maintained between 23–25 torr. Osmotherapy is given whenever the intracranial pressure exceeds 23 torr, using the minimal

effective dose of mannitol (0.25–0.50 g/kg). All patients receive dexamethasone (1.0–1.5 mg/kg·day) in divided 6-h doses. If patients are refractory to osmotherapy, venting of cerebrospinal fluid through the ventriculostomy catheter is attempted. Fluid and electrolyte requirements are adjusted every 2–4 h according to urine output, and serum and urine electrolytes and osmolalities. Blood sugars are monitored hourly to prevent marked hyperglycemia or hypoglycemia. Blood glucose levels are maintained between 150–250 mg/dl. When blood sugar levels are over 400 mg/dl, low-dose continuous infusions of insulin are given. Hyperthermia is prevented by placing patients with temperature elevations above 37.5°C on a cooling mattress. Changing patterns of EEG recordings are used to assess neuromuscular blockade.

SUBJECTS AND METHODS

Sixteen of 18 survivors of Reye's syndrome cared for at Rainbow Babies and Children Hospital between 1974 and 1979 (Table 1) were seen for a follow-up evaluation which included intellectual and behavioral assessment. All patients had been under the medical care of one of the authors (M.W.L.). Informed consent was obtained from all parents and from children 9 yr of age or older. The 2 survivors who were not seen for follow-up included 1 child whose family did not respond to our requests for follow-up and an 18-yr-old male currently in the Armed Forces and stationed overseas.

Psychological Testing

All children were administered intelligence tests. The 2 youngest children were administered the Stanford-Binet Intelligence Scale. Children between the ages of 7–15 yr (N = 10) were administered the Wechsler Intelligence Scale for Children—Revised (WISC-R), and subjects 16 yr of age and older (N = 4) were administered the Wechsler Adult Intelligence Scale (WAIS). The WISC-R and WAIS consist of multiple subtests which can be summed for the verbal and performance subtests to yield the Verbal and Performance IQs or for all subtests to yield a full-scale IQ or measure of general intelligence.

Mothers of children between the ages of 7–16 (N = 11) rated their children with the Achenbach Child Behavior Checklist (CBL).[13, 14] The CBL consists of 146 items dealing with school, social, and activity variables, as well as indices of psychopathology. The CBL yields a series of standardized Child Behavior Profiles containing behavior problem scales (e.g., schizoid, depressed, uncommunicative, obsessive-compulsive, somatic complaints, withdrawn, hyperactive, aggressive) and three competence scales (school, activities, social). The behavior problem and competence scales are expressed as normalized standard T scores. The T score has a mean of 50 and standard deviation of 10. Thus, a T score of 70 indicates that a subject has scored 2 standard deviations above the mean.

Interview

The mothers of the study children were asked 65 questions dealing with the following general areas of parental perceptions and concerns: events and symptoms before the diagnosis of Reye's syndrome; the actual diagnosis of Reye's syndrome (where, by whom, information conveyed to parents); care of the child on the PICU; parental attitudes toward medical staff; parents'

TABLE 1. Illness variables

Subject	Sex	Age at admission (yr-months)	Age at follow-up (yr-months)	Stage of illness[a]	Blood ammonia (mg/dl)	No. of exchange transfusions
1	F	1–7	2–2	4	300	0
2	F	2–0	2–3	4	500	0
3	M	4–3	9–7	4	57	4
4	M	4–9	7–1	4	310	4
5	M	6–0	8–5	4	505	7
6	M	7–2	7–6	4	143	0
7	F	7–4	9–10	4	270	12
8	M	9–0	15–0	4	320	0
9	M	9–3	12–9	2	227	0
10	M	10–3	13–9	2	174	0
11	F	12–0	16–4	4	138	5
12	F	13–1	18–5	4	221	6
13	M	14–10	19–8	2	111	0
14	M	15–2	19–6	4	258	5
15[b]	F	8–0	13–5	4	264	4
16[a]	M	5–4	7–6	4	297	4
Totals		8.13 ± 4.18	11.44 ± 5.57	3.63 ± 0.81	255.86 ± 123.50	3.19 ± 3.47

[a] Brunner et al.[9]
[b] Diagnosed as mentally retarded prior to onset of illness
[c] Diagnosed with psychomotor developmental delay prior to onset of illness

worries during the acute phase of the illness and convalescence; adjustment after hospital discharge; and current adjustment and concerns. All interviews were tape-recorded and transcribed for data analysis. Only mothers were interviewed because, in a majority of cases, fathers were not available at the times the interviewer could meet with them.

RESULTS

Neurological and Intellectual Findings

No children had severe neurological or physical residua. All but 2 children (Table 2) had IQ within the low normal to bright range. The two exceptions were children who had been diagnosed as mentally retarded before the onset of Reye's syndrome. One child had attended preschool classes for the developmentally delayed before this illness, whereas the other had a history of microcephaly and had been in public school classes for the mentally retarded. Their scores on IQ tests were excluded from statistical analysis. Apart from these two cases, no children had failed a grade or were in any special remedial programs. All were doing at least average work in school and several were in accelerated learning classes or programs for gifted students.

Utilizing a Spearman rank-order correlation corrected for ties, there was a significant relationship ($r_s = 0.677$, $p < 0.01$) between age of onset of illness and full-scale IQ, with younger subjects achieving lower IQs. For subjects between the ages of 7–13 yr, performance IQs were significantly lower than verbal IQs ($T = 3.634$, $p < 0.01$) The 4 subjects of 16 yr or older had higher performance IQs than verbal IQs; however, the small number of subjects in this group precluded statistical analysis. There was no relationship between IQ and sex, socioeconomic status, duration since hospitalization, number of exchange transfusions, or clinical grade of illness.

Emotional Adjustment

Seven (44%) children showed no emotional or behavioral problems either by checklist or interview (Table 2). Nine (56%) children had emotional problems lasting longer than 3 months after hospital discharge. Seven (44%) children achieved significant T-scores (T score > 70) on at least one scale of the Achenbach Child Behavior Profile; these children also were reported by their mothers to have problems. Two subjects above the age range for the CBL also had emotional problems by maternal report. The problems reported included primarily nonorganic somatic complaints, anxiety, depression, and to a lesser degree, withdrawal and uncommunicativeness.

TABLE 2. Follow-up data

Subject	Verbal IQ	Performance IQ	Full-scale IQ	Achenbach Child Behavior Profile[a]	Emotional sequelae children[b]	Emotional sequelae mothers[b]	Previous losses[b]
1			88	NA		X	
2			92	NA		X	X
3	88	82	84	SC,U,OC,SW, H,ACT	X	X	
4	111	104	108	U	X		
5	109	88	100	SC	X	X	X
6	125	121	126	SC	X	X	
7	113	98	106	WNL		X	X
8	101	100	101	WNL		X	X
9	108	101	105	SC	X	X	X
10	112	97	105	WNL		X	
Mean ± SD	108.4 ± 10.61	98.9 ± 11.52	102.2 ± 11.52				
11	113	124	119	WNL		X	X
12	96	123	108	NA	X	X	X
13	107	113	110	NA		X	X
14	124	133	130	NA	X	X	X
Mean ± SD	110 ± 11.69	123.3 ± 8.18	116.7 ± 10.05				
Mean ± SD of subjects 1–14	108.83 ± 10.47	107.00 ± 15.71	105.86 ± 13.11				
15	52	45	44	ACT,SOC,S	X	X	
16	73	85	77	SC,UC,OC,S	X	X	X
					9/16	15/16	10/16

[a] Abbreviations: NA = not administered; U = uncommunicative; SW = social withdrawal; A = aggressive; SOC = decreased social participation; SC = somatic complaints; OC = obsessive-compulsive; H = hyperactive; ACT = decreased activities; S = school problems.

[b] As reported by mother.

One child was reported to have problems with aggression and impulse control. Although we had seen the surviving children only for intellectual assessment and had relied on mothers for information about their child's emotional status, several children spontaneously broached the subject of their emotional reactions while taking their IQ tests. One subject, 15 yr old when hospitalized with Reye's and 19 yr old at follow-up, spoke movingly of having felt depressed and fearful for 2 yr after his illness. Despite reassurances that he had recovered, he had continued to worry about a recurrence of the illness, to suffer from nightmares about the ICU and to feel "different" from other children. Although he was a bright young man who did well in school and had been accepted at a good private college, he believed that he would have performed even better at school had he not been so preoccupied with his illness.

During the interview, 14 (88%) mothers reported that they had suffered from anxiety, depression, and/or overprotective behavior lasting from 6 months to as long as 5 yr after their child's illness. Although no questions were included in the interview regarding previous deaths or severe illnesses within the family, 10 (63%) mothers spontaneously reported previous losses involving the death or severe debilitating illness of family members. Several mothers had earlier lost their own siblings to illness. Thirteen (81%) mothers reported that during the time their child had been in the ICU, they had, at some point, expected their child to die. Five (31%) mothers cited fear that their child would be brain-damaged as a major worry and preoccupation during and after the child's illness.

Perceptions of Care

All mothers indicated that they had stayed at the ICU continuously (except for trips home for change of clothes, etc.) during their child's illness and favored this arrangement. All felt positively about the physicians' truthfulness about the disease, prognosis, and treatment. Despite our concerns about the large number of physicians from various subspecialties dealing with the children and families, no parents indicated difficulty dealing with several physicians. In fact, several families indicated that well-coordinated input from many professionals had been reassuring to them. All married partners indicated that they had received their main support from spouses during their child's illness, whereas all single parents felt generally unsupported.

Despite their intense concerns, all but 2 families indicated that they had not missed psychological or social work intervention during the acute phase of their child's illness. During the acute illness, they had wanted clear and regular medical feedback and all felt satisfied that they had received it. Twelve (75%) of the 16 mothers indicated that they would have liked an opportunity to explore their emotional reactions at a later date, possibly as a part of medical follow-up visits.

DISCUSSION

Although preillness IQs were not available for our subjects, the results of our study indicate that neurological, intellectual, and academic outcomes may be very good for recent survivors of Reye's syndrome. Younger survivors may be somewhat more vulnerable to intellectual sequelae of the illness,[8] particularly in nonverbal intellectual abilities. However, in no case were the problems severe enough to warrant special class placement for any of the school-age children.

In striking contrast to the relatively good intellectual and academic recovery were the significant emotional problems of both the children and their families. Surviving children exhibited nonorganic somatic complaints, anxiety, and depression. The mothers, to an even greater extent than the children, experienced significant and longstanding emotional reactions.

The reactions of the surviving children and their mothers were similar to those described by Solnit and Green[15] in their study of the vulnerable child syndrome and by Benjamin[12] in her study of children surviving acute illness. In Benjamin's study, parents and children continued to worry about their "close call." Parents displayed anticipatory grief during their child's illness and incomplete mourning after the child's recovery. Segal and Gagnon[16] note that the severity of these problems increases with the actual severity of the child's illness. They found that pediatricians and parents may be at variance with one another with respect to the timing and amount of concern about a recovering child's physical and emotional well being. Our experience suggests that parents and children continue to be preoccupied with the illness long after the child's physical recovery, while the physician, pleased with a "successful" outcome, may not deal adequately with the families' lingering concerns. Readjustment problems after Reye's syndrome may be longstanding. Thus, the specialist or primary care physician providing follow-up medical care should be alert to the potential for continued familial disruption.

Previous losses and unresolved grief also may become potent determinants of continued parental preoccupation with the child and development of emotional sequelae in survivors. The medical history-taking should include not only attention to acute illness data but a more thorough attempt to document previous losses and to discuss them with parents. An audit of our own hospital records indicated that such material was rarely asked for or elicited during the child's hospitalization.

For parents, the acute phase of Reye's syndrome represents a traumatic experience. Its sudden onset and unpredictable course allow no time for the mobilization of adaptive defenses. The monitoring equipment, exchange transfusions, muscle paralysis, barbiturate coma, etc., which are included in the management of many Reye's victims, are, in themselves, overwhelmingly frightening procedures for parents, even when they have been given preparation and explanation for procedures.

It is, therefore, vital to assess and reassess not only mortality but also morbidity rates over the time in order to give parents realistic information. At our own institution, the prognosis for survivors of Reye's syndrome is better than might have been assumed from even some of the more recent studies reported in the literature. Because fear of brain damage was a major preoccupation of parents in our study, we believe that it is important to acquire accurate information regarding CNS morbidity, and, where warranted, to help parents set aside those concerns.

Parents also can be helped by a chance to air their emotional concerns. However, during the acute phase of the child's illness, such an intervention may come to families as more of a demand or burden than an opportunity. Parents want close medical feedback and supervision at this early phase and wish more intensive psychosocial intervention at a later time as the child begins to recover.

This follow-up study has been limited to assessment of surviving children and their mothers, thereby excluding information about the roles of fathers. Ideally, evening or weekend appointments should be offered in order to increase the likelihood of paternal participation. Furthermore, some of the emotional and behavior problems the mothers reported of their children may reflect the increased scrutiny of surviving children by their parents. Future research should, therefore, include independent corroboration of parental report perhaps by teacher ratings, direct psychological assessment of survivors, or comparison of surviving children with a sibling control group.

REFERENCES

1. Reye RDK, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. *Lancet* 1963; 2:749
2. Mowat AP: Encephalopathy and fatty degeneration of the viscera: Reye's syndrome. *Arch Dis Child* 1973; 48:411
3. Bradford WD, Latham WC: Acute encephalopathy and fatty hepatomegaly. *Am J Dis Child* 1967; 114:152
4. Devivo D, Keating JP: Reye's syndrome. *Adv Pediatr* 1976; 22:175
5. Davidson PW, Willoughby RH, O'Tuama LA, et al: Neurological and intellectual sequelae of Reye's syndrome: A preliminary report. In: *Reye's Syndrome.* Pollack JD (Ed). New York, Grune and Stratton, 1975, pp 55–59
6. Trauner DA: Treatment of Reye's syndrome. *Ann Neurol* 1980; I:2
7. Bobo RC, Schubert WK, Partin JC, et al: Reye syndrome: Treatment by exchange transfusion with special reference to the 1974 epidemic in Cincinnati, Ohio. *J Pediatr* 1975; 87:881
8. Davidson PW, Willoughby RH, O'Tauma LA, et al: Neurological and intellectual sequelae of Reye's syndrome. *Am J Ment Def* 1978; 6:535
9. Brunner RL, O'Grady DJ, Partin JC, et al: Neuropsychologic consequences of Reye syndrome. *J Pediatr* 1979; 95:706
10. Shaywitz BA, Rothstein P, Venes JL: Monitoring and management of increased intracranial pressure in Reye syndrome: Results in 29 children. *Pediatrics* 1980; 66:198
11. Shaywitz BA, Leventhal JM, Kramer MS, et al: Prolonged continuous monitoring of intracranial pressure in severe Reye's syndrome. *Pediatrics* 1977; 59:595
12. Benjamin PY: Psychological problems following recovery from acute life-threatening illness. *Am J Orthopsychiatry* 1978; 48:284
13. Achenbach TM: The child behavior profile: I. Boys aged 6–11. *J Consult Clin Psychol* 1978; 46:478
14. Achenbach TM, Edelbrock CS: The child behavior profile: II. Boys aged 12–16 and girls aged 6–11 and 12–16. *J Consult Clin Psychol* 1979; 47:223
15. Green M, Solnit A: Reactions to the threatened loss of a child: A vulnerable child syndrome. *Pediatrics* 1964; 34:58
16. Sigal J, Gagnon P: Effects of parents' and pediatricians' worry concerning severe gastroenteritis in early childhood on later disturbance in the child's behavior. *J Pediatr* 1975; 87:809