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Nonalcoholic Cirrhosis Associated With Neuropsychological Dysfunction in the Absence of Overt Evidence of Hepatic Encephalopathy

RALPH E. TARTER, ANDREA M. HEGEDUS, DAVID H. VAN THIEL, ROBERT R. SCHADE, JUDITH S. GAVALER, and THOMAS E. STARZL
Departments of Psychiatry, Medicine, and Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

Although much is known about the neuropsychological functioning of cirrhotic individuals with Laennec's (alcohol associated) cirrhosis, little is known about the neuropsychological functioning of individuals with nonalcoholic cirrhosis. In the present investigation, we have determined that individuals suffering from chronic nonalcoholic cirrhosis, despite the absence of clinical signs of hepatic encephalopathy, are impaired on neuropsychological tests that measure visuopractic capacity, visual scanning, and perceptual-motor speed. In contrast, intellectual, language, memory, attentional, motor, and learning abilities are intact. In comparison with a chronically ill control group of patients suffering from Crohn's disease, individuals with advanced nonalcoholic cirrhosis exhibit less emotional disturbance, but are more impaired in their daily activities. These findings indicate that individuals with nonalcoholic cirrhosis, even in the absence of overt clinical signs of encephalopathy, manifest neuropsychological impairments and experience significant disruption in the routines of everyday living.

For the latent or subclinical condition of hepatic encephalopathy in particular, neuropsychological testing procedures (psychometric measures) have been found to be more sensitive indicators of the disorder than is the electroencephalogram (1–3). Moreover, they have been shown to be better at detecting subtle cerebral pathology than are routine clinical neurological examinations, skull x-rays, and cerebral angiograms (4). Previous neuropsychological investigations that have implicated cerebral dysfunction in patients with cirrhosis have been limited by the fact that they either (a) studied a small number of subjects, (b) tested a limited range of psychological processes, (c) evaluated patients who were receiving medication, or (d) only examined patients who had undergone surgical interventions or had a history of alcoholism; factors that, in and of themselves, might have been responsible for impairments that were detected (1,2,5–9).

Inasmuch as emotional stability and neuropsychological competency (e.g., communication ability, perceptual-motor coordination, problem-solving skills) are basic requirements for successful everyday living, a comprehensive neuropsychiatric evaluation, which would increase our understanding of the effects of hepatic disease on such functional capacities, would be important in patient management decisions. The information accrued from such testing would be particularly valuable in assisting the physician making decisions in areas in which the vocational, social, and psychiatric aspects of the disease might be considered important.

Methods

Subjects

Thirty biopsy-confirmed cases of chronic nonalcoholic cirrhosis comprised the experimental group. The group consisted of 18 patients with primary biliary cirrhosis and 12 patients with postnecrotic cirrhosis. All members of the group were inpatients at Presbyterian Universi-

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Address requests for reprints to: Ralph E. Tarter, Ph.D., 3811 O'Hara Street, Pittsburgh, Pennsylvania 15213.
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Table 1. Scores of the Nonalcoholic Cirrhosis Subjects on Selected Laboratory Parameters Documenting Liver Disease

Laboratory test	Normal values	Nonalcoholic cirrhosis subjects $\bar{x}$	SD
Alanine transaminase	<37 IU/L	343.60 IU/L	928.07
Asparate transaminase	<34 IU/L	218.80 IU/L	598.36
Alkaline phosphatase	<100 IU/L	802.36 IU/L	812.82
Bilirubin, total	0.3–1.5 mg/dl	10.61 mg/dl	10.72
Bilirubin, direct	<0.4 mg/dl	7.74 mg/dl	8.81
Albumin	3.5–5.0 g/dl	3.31 g/dl	0.63
Globulin	1.3–1.7 g/dl	3.25 g/dl	0.99
Prothrombin time	10.8–12.8 s	13.23 s	2.40
Indocyanine green serum (level at 20 min[a])	<0 mg/ml at 20 min	48.86 mg/ml	31.34
Fasting ammonia level	9.0–41.0 μm/L	38.70 μm/L	14.39

[a] 0.5 mg/kg given i.v. at time zero.

ty Hospital in Pittsburgh, Pennsylvania. The group had a mean age and education level of 40.93 (s = 8.60) and 13.73 (s = 2.53) yr, respectively. None of the patients had a history of alcohol or drug abuse, neurological injury or disease, or psychiatric disorder. In addition, none of the subjects have had shunt surgery, nor did any of them exhibit overt clinical signs of hepatic encephalopathy. Chronicity of their illness, estimated from the time of the first diagnosis to the time of this evaluation, was 3.81 yr. Table 1 presents the results of the various laboratory parameters that quantify the severity of the hepatic dysfunction present in these subjects.

A chronic-illness control group consisting of 10 patients suffering from Crohn's disease was studied also. They were selected as the comparison group because they had a chronic medical illness, often received the same medications, and were treated by the same physicians as the patients with cirrhosis. Moreover, this group of subjects also controls for any nonspecific effects that a chronic illness has on neuropsychiatric functioning. Most of the patients in the control group, on at least one occassion, had been treated as an inpatient, but were under medical care on an outpatient basis at the time of the evaluation. Moreover, none of the subjects in the Crohn's disease control group had a history or biochemical evidence of liver disease, alcohol or drug abuse, or neurological disease or had been treated for a psychiatric disorder. They had a mean age of 39.30 (s = 11.82) yr and an educational level of 14.90 (s = 2.88) yr. Their mean disease chronicity was 5.29 yr. None of these factors differed from those present in the liver disease study group. No member of either group was taking medications (e.g., steroids, neuroleptics) that are known to impair cognitive capacity.

Procedures and Analyses

Once a specific hepatic diagnosis was established using clinical, biochemical, and serologic data, and confirmed by liver biopsy, the liver disease patients were administered a battery of neuropsychological, psychiatric, and psychosocial measures. The neuropsychiatric examination was conducted without the tester's awareness of the medical diagnosis.

The neuropsychological battery was designed to meet three criteria: replicability, comprehensiveness, and validity. The tests that were selected have been demonstrated previously to identify impairments in patients with various forms of cirrhosis (1,2,5–9). In order to yield a more comprehensive profile of intellectual, attentional, memory, language, learning, perceptual-motor, and spatial processes, it also was necessary to extend the range of functions that had been measured by previous investigations. The specific tests used to evaluate these neuropsychological processes are listed in Table 2 in Results. Only tests that have been validated to detect cerebral dysfunction were included in the test battery (10,11).

Administration of the test battery required ~2.5 h. In order to circumvent any possible confounding effects of fatigue that may affect the test performance, the testing was conducted over two individual 75-min sessions separated by a day of rest. Subjects completed the following three questionnaires between the two test days: Minnesota Multiphasic Personality Inventory (MMPI),* the Sixteen Personality Factors Questionnaire (16PF),† and the Sickness Impact Profile (SIP).‡

The tests were scored according to standardized procedures. The neuropsychological battery listed in Table 2 contains separate verbal (Peabody Picture Vocabulary Test) and nonverbal (Raven's Progressive Matrices) measures of intelligence quotient (IQ). The attention and concentration test scores indicate the longest sequence of digits that the person could recall accurately, immediately after their presentation. The mental control score is a combined index of speed and accuracy in counting backwards, reciting the alphabet, and performing serial additions. An index of nine is the maximum score on this test.

The learning and memory tests of the Weschler Memory Scale were scored according to standard procedures for the immediate recall components, and the same criteria were

* The Minnesota Multiphasic Personality Inventory is a clinically standardized quantitative test of psychopathology and personality disturbance. † The Sixteen Personality Factors Questionnaire is a standardized quantitative measure of normal personality functioning across 16 different dimensions. ‡ The Sickness Impact Profile is a quantitative and validated health status assessment scale that measures the percentage of impairment due to an illness on behavioral functioning and social adjustment.

used for scoring the subject's performance upon delayed recall; i.e., 30 min later. The logical memory test score reflects the number of items recalled verbatim from two brief passages that are orally presented. The maximum score is 23. The figural memory test score describes the capacity to reproduce four simple figures from memory after a 10-s exposure to each stimulus. A score of 14 indicates perfect recall. The paired-associate learning test measures the capacity to learn a 10-item list of word pairs in three trials. A weighted score between 0 and 21 is obtained which takes into account differences in item difficulty. The delayed recall score on this test describes the number of correct associations remembered. The supraspan score describes the number of trials it took the subject to learn a sequence of digits that exceeded the digit span score by one extra digit. For example, if the person's digit span was found to be six, the number of trials it took the subject to learn a seven-digit string was determined.

The finger tapping score is the combined number of taps on a telegraph key in a 10-s period using the preferred and nonpreferred hands. The mean of five trials was obtained for each hand and the scores summed to give a measure of motor speed. The Purdue Pegboard is the summed score of the right and left hands and bimanual performance. It describes the number of pegs placed in a pegboard in a 30-s time period. The two Star Tracing Test scores represent the time it took to draw the outline of a six-pointed star and the number of errors made. An error in motor control was recorded every time the tracing touched or deviated outside of a 0.25-in. boundary. The Symbol Digit Modalities Test score is the total number of correct sequential matchings of numbers to symbols in a 90-s interval.

The block design test, adapted from the Wechsler Adult Intelligence Scale, yields a weighted index combining speed and accuracy. It describes the ability to construct designs or patterns from pictorial models. The maximum score is 24. The Tactual Performance Test time score describes the time it takes the subject, while blindfolded, to place 10 geometrically shaped blocks in a formboard. The memory score on this test reflects the number of block shapes that the person is able to recall after completion of the task. The location score describes the accuracy of the subject's perspective of where the 10 blocks belonged in the formboard. On these latter two measures, 10 is the maximum score for each. The Trailmaking Test score is the total time it took the subject to complete both parts of the test. The first part involves sequentially connecting numbers arranged haphazardly on a page, whereas the second part requires the person to connect alternating numbers and letters.

The language tests, selected from the Boston Diagnostic Aphasia Examination, were scored according to standard procedures. The fluency score is the number of different animals that the person could name in 60 s. The confrontation naming score describes the ability to name a variety of pictures, colors, letters, and objects. The maximum score on this test is 105. The responsive naming test score indexes oral communication ability. A score of 30 is a perfect performance. The phrase repetition test requires the subject to repeat simple and complex phrases. A score of eight on each part is a perfect performance. The Token Test measures comprehension capacity. The test score reflects the number of correct responses in executing simple commands from the examiner (e.g., put the green square next to the red circle). A score of 13 indicates a perfect performance.

The MMPI contains three validity scales and 10 clinical scales. The validity scales measure the response set of the subject while answering the test questions. The lie scale (L) illustrates if the person is being intentionally deceptive, whereas the F scale and the K scale reveal if the person is emphasizing more negative or positive aspects of themselves, respectively. The hypochondriasis scale (HS) measures the severity of visceral symptoms, whereas the hysteria scale (HY) assesses the severity of somasthetic complaints. The depression scale (D) quantifies the severity of symptoms for this disorder. The psychopathic-deviate scale (PD) assesses antisocial behavior and tendencies toward social nonconformity. The masculinity–femininity scale (MF) describes the attitudes, interests, and feelings that are typically associated with each gender. The paranoia scale (PA) quantifies the person's defensiveness and delusional perceptions. The psychasthenia scale (PT) measures obsessional anxiety, compulsiveness, and introspective worry. The schizophrenia scale (SC) quantifies the number of symptoms associated with this type of psychosis, as well as certain other disturbances related to self-esteem and interpersonal functioning. The hypomania scale (MA) describes the amount of behavioral activity and energy expended by the person. The social introversion scale (SI) measures the person's motivation for social interaction. All of the scales were scored according to the standard format and then converted to T scores ($\bar{x} = 50$, $s = 10$). The higher the score, the more severe is the psychopathology.

The 16 PF measures 16 dimensions of personality. The raw scores for each scale are converted into a standard nine (stanine) score, with a mean of five. Each of the personality traits, presented in Figure 2, is conceptualized as lying along a bipolar dimension. The greater the deviation from the mean score of five, the more strongly expressed is the particular personality trait.

The SIP describes the percentage of impairment across 12 categories of daily functioning. These are social interaction, sleep and rest, ambulation, eating, work, home management, mobility, body care, communication, recreation and pastimes, alertness, and emotional behavior. Three summary scores measuring physical dysfunction, psychological dysfunction, and total dysfunction also are obtained.

Statistical Methods

The nonalcoholic cirrhosis and Crohn's disease groups were compared using two-tailed univariate Student's *t*-tests for independent samples.

Results

The patients with nonalcoholic cirrhosis performed less well than the Crohn's disease controls

on the Symbol Digit Modalities Test, a measure of speed of visual scanning and repetitive motor responding ($t = 3.39$, $p < 0.01$). The subjects with cirrhosis also had more difficulty assembling blocks into various spatial configurations than did the controls ($t = 1.90$, $p < 0.06$). In addition, the individuals with cirrhosis performed less well than the controls on the Purdue Pegboard, a test of perceptual-motor speed ($t = 2.78$, $p < 0.01$). Moreover, they took longer than the controls to perform the Trailmaking Test ($t = 2.10$, $p < 0.05$). The patients with cirrhosis took more time to complete the Tactual Performance Test than did the controls ($t = 2.33$, $p < 0.05$). After the task was completed, the subject had the blindfold removed and was required to draw from memory the shapes of the blocks, as well as their location in the formboard. Although no difference in remembering the shapes of the blocks was noted, the patients with cirrhosis were less capable of remembering their spatial location in the formboard than were the controls ($t = 2.34$, $p < 0.05$).

In contrast to the perceptual-motor speed tests, simple motor speed tasks were unimpaired in individuals with nonalcoholic cirrhosis when compared to the controls. Thus, both the cirrhosis and the Crohn's disease subjects performed equally well on tests of speed of finger tapping and time taken to draw a star. None of the language tests discriminated the cirrhosis patients from the Crohn's disease patients. Responsive naming, phrase repetition, and confrontation naming were not found to differ significantly between the two study groups.

In Table 2, it can be seen that the two groups performed equally well on tests of cognitive capacity. Specifically, measures of verbal and nonverbal intelligence did not discriminate between the two. Moreover, memory capacity, measured by the immediate and delayed recall scores of verbal and figural information from the Wechsler Memory Scale, and performance on the tests of attention and concentration were similar for the two groups.

In terms of the psychiatric status as measured by the MMPI, the cirrhotic patients did not exhibit more disturbance than the patients with Crohn's disease. This indicates that the deficits reported for the cirrhotic group cannot be explained simply on the basis of their being more emotionally disturbed. In Figure 1, it can be seen that the individuals with cirrhosis did not score in the pathognomonic ranges ($T > 70$) on any of the clinical scales of the MMPI. Comparisons of the two groups revealed that they differed only on the Social Introversion Scale ($t = 3.05$, $p < 0.01$), with the Crohn's disease subjects scoring in the more pathological direction.

On the 16 PF, a test of personality adjustment, it was found that the Crohn's disease patients reported slightly more disturbances than did the patients with nonalcoholic cirrhosis. The results, presented in Figure 2, indicate that the Crohn's disease patients described themselves as being more sober in attitude ($t = 2.26$, $p < 0.05$) than the patients with cirrhosis. In addition, they tended to be less emotionally stable ($t = 2.01$, $p < 0.06$) and more apprehensive ($t = 1.97$, $p < 0.06$) than the cirrhosis patients.

Figure 3 presents the results for the two groups on the SIP. Several measures in this profile differentiated the two groups. The patients with nonalcoholic cirrhosis reported more disturbances of sleep and rest ($t = 2.03$, $p < 0.05$), body care and movement ($t = 2.09$, $p < 0.05$), recreation and pastimes ($t = 2.32$, $p < 0.05$), and experienced more physical dysfunction ($t = 1.98$, $p < 0.06$) than did the Crohn's disease patients. Thus, the patients with cirrhosis were

Table 2. Means and Standard Deviations of the Neuropsychological Measures of the Nonalcoholic Cirrhosis and the Crohn's Disease Subjects

	Nonalcoholic cirrhosis		Crohn's disease	
Capacity/measure	$\bar{x}$	s	$\bar{x}$	s
Verbal Intelligence (IQ)				
Peabody Picture Vocabulary Test	97.00	11.61	99.00	15.81
Nonverbal Intelligence (IQ)				
Raven's Progressive Matrices	110.28	13.64	114.50	13.21
Attention and Concentration				
Digit span forward	6.43	1.41	7.22	0.97
Digit span backward	4.72	1.39	4.78	1.30
Mental control	7.70	1.57	7.90	0.99
Learning and Memory				
Logical memory (immediate)	17.57	5.13	19.40	6.65
Logical memory (delayed)	12.83	6.24	13.10	6.40
Figural memory (immediate)	9.89	3.15	10.40	2.76
Figural memory (delayed)	10.83	2.39	10.40	3.89
Paired associates (immediate)	16.72	2.64	17.75	2.06
Paired associates (delayed)	9.20	1.03	9.20	1.14
Supraspan (digit span +1)	2.87	1.80	2.22	1.72
Perceptual-Motor				
Finger tapping (right & left)	86.43	11.42	81.80	12.71
Purdue Pegboard (right & left)	25.80	5.24	29.22	2.95
Star tracing				
-time (right & left)	52.03	13.72	43.90	25.02
-error (right & left)	2.67	4.38	1.30	1.49
Symbol digit modalities	42.87	13.04	53.50	6.45
Spatial				
Block design	17.37	5.08	21.30	5.87
Tactual performance				
-time (s)	1148.73	490.54	835.40	297.01
-memory	6.85	1.92	7.70	1.49
-location	2.92	2.27	4.90	2.28
Trailmaking (parts A & B)	128.23	57.90	88.67	46.79
Language				
Boston Diagnostic Aphasia Exam				
Fluency	21.77	6.47	23.80	5.98
Confrontation naming	104.73	0.83	103.70	1.70
Responsive naming	30.00	0.00	29.90	0.31
Token Test	12.00	1.39	12.30	0.82

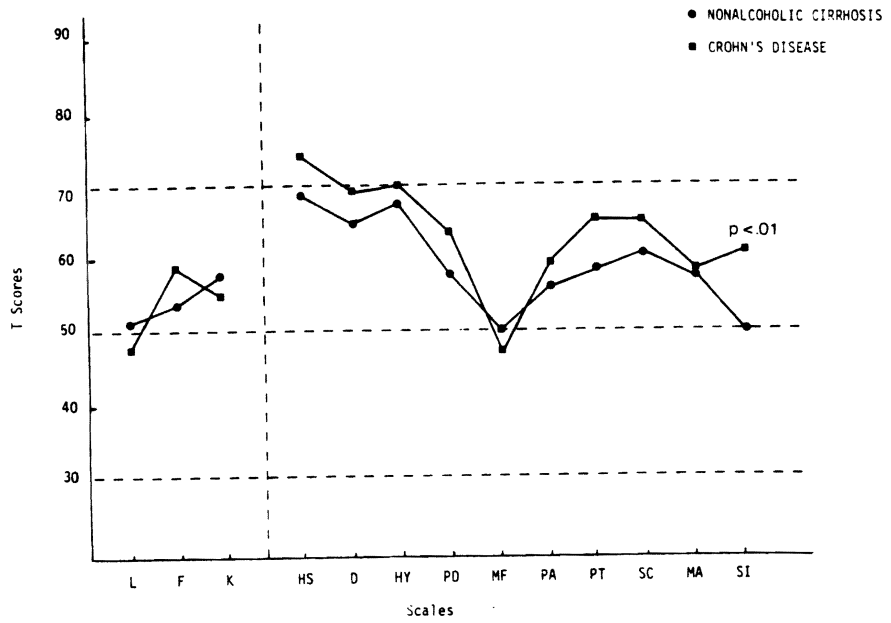

Figure 1. Profiles of the nonalcoholic cirrhosis patients and the Crohn's disease subjects on the Minnesota Multiphasic Personality Inventory (MMPI). The population norm is 50, and a score >70 is pathognomonic.

found to be affected more adversely by their disease on certain aspects of daily living than the Crohn's disease subjects, a finding which is consistent with the more life-threatening nature of the illness in the former group.

Discussion

The major finding of this study is that patients suffering from nonalcoholic cirrhosis, despite normal mental status upon clinical examination, demonstrate a number of quantifiable neuropsychological deficits. The impairments identified were noted on tasks that required perceptual-motor efficiency or visuopractic capacity, or both. These impairments cannot be attributed to disturbed intellectual, memory, or motor processes inasmuch as the two groups being compared did not differ on these measures.

It is interesting to note that the same type of neuropsychological impairments exhibited by the patients with nonalcoholic cirrhosis identified in this study also are often found in individuals who have verified lesions in the frontal-parietal regions of the brain (10,11). In the absence of direct histological information, which is unobtainable in living subjects, it was not possible to confirm the localization of brain pathology in the subjects of this investigation. However, histopathological analyses of the brains of patients who died in hepatic coma have revealed widespread changes, including a proliferation of Alzheimer type II cells that are most pro-

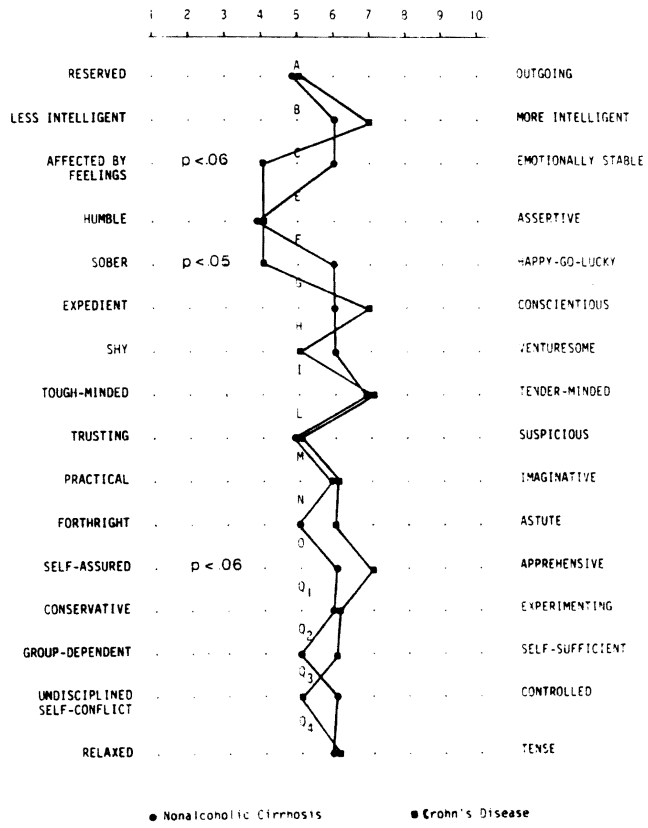

Figure 2. Profiles of the nonalcoholic cirrhosis patients and the Crohn's disease subjects on the 16 Personality Factors Questionnaire (16PF). The population norm is 5, from which a plus or minus 2 SD is considered implicative of the respective personality trait.

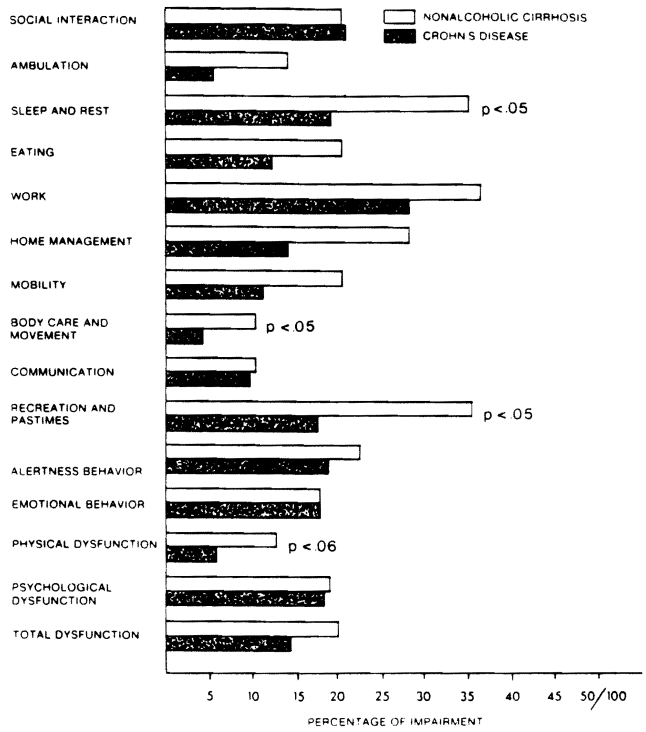

Figure 3. Profiles of the nonalcoholic cirrhosis patients and the Crohn's disease subjects on the Sickness Impact Profile (SIP). The higher the score, the greater the adverse impact of the illness on daily functioning.

nounced in the frontal-parietal brain regions (12,13).

Furthermore, it is noteworthy that chronic alcoholics without liver disease have been found to perform poorly on the same types of measures that were used in this investigation (14,15). Whether the neuropsychological deficits exhibited by such alcoholics are the consequence of hepatic dysfunction or the neurotoxic effects of ethanol, or both, would thus appear to merit further investigation. Although it has been established clearly that ethanol is neurotoxic in animals, its relative contribution to the spectrum of neuropsychological impairments in humans who abuse alcohol is as yet unknown. Rehmstrom et al. (16) have reported that nonalcoholic cirrhotics performed similarly to alcoholics with cirrhosis on tests of learning, memory, perceptual-motor speed, and visuospatial organization, leading these authors to conclude: "The most important factor in encephalopathy in a person with both cirrhosis and alcoholism seems most often to be the cirrhosis and not the direct alcoholism brain damage" (16). However, it should be noted that their nonalcoholic sample consisted of only 7 subjects. Therefore, their results should be interpreted quite cautiously; although, for the most part, our findings confirm the results of this latter investigation.

In another study, Gilberstadt et al. (1) found that alcoholics with cirrhosis performed less well than alcoholics without cirrhosis on several psychomotor tests. Other investigators also have noted greater impairment in cirrhotic than noncirrhotic alcoholics (2,17). These latter studies, in conjunction with the present findings, illustrate that hepatic dysfunction is associated with neuropsychological impairments, but the exact nature of these putative hepatic effects in relation to the contribution of the adverse effects of direct ethanol neurotoxicity remains to be clarified.

Although perceptual-motor and visuopractic deficits were manifested by the patients with cirrhosis, it should be noted that the absolute magnitude of these impairments was of only moderate severity. Whether these impairments actually affect the capacity of the cirrhotic patients to perform routine activities (e.g., driving an automobile, doing manual tasks) cannot be ascertained. The findings from the SIP certainly raise this possibility, however, and suggest the need for further investigation.

The observation that the cirrhosis group exhibited less personality and psychiatric disturbances than did the chronically ill disease control Crohn's group illustrates that the neuropsychological deficits identified in the former group are not due simply to emotional disturbances. Indeed, the patients with cirrhosis described their emotional status quite favorably, despite the advanced nature of their hepatic disease.

Nonalcoholic cirrhosis, however, adversely affects routine everyday functioning and social adjustment. The SIP, a measure of how much an illness limits daily routine, is not merely a test of disease severity. For example, a broken thumb in a surgeon exerts a more deleterious effect on daily routine and psychosocial adjustment than the same injury incurred by someone who does not rely on manual dexterity. In addition, certain benign and transient conditions (e.g., the flu) could have a greater impact on daily routine than more serious, and even more life-threatening disorders (e.g., hypertension). The point to be made is that the impact of an illness is not synonymous with severity. In this investigation, it was demonstrated that nonalcoholic cirrhosis, a potentially fatal condition, was associated with only a 20% level of dysfunction, which was not significantly different from that of a rarely fatal Crohn's disease group. Thus, overall impact between the groups did not differ. However, on certain specific aspects of daily functioning (sleep and rest, body care and movement, physical dysfunction, and recreation and pastimes), the cirrhotic patients revealed a greater impairment of behavior by their illness than the Crohn's patients, a finding that is not merely due to greater illness severity, or attributable to their inpatient status when compared to the Crohn's subjects.

The demonstration of neuropsychological impairment in persons suffering from nonalcoholic cirrhosis without clinical signs or symptoms of hepatic encephalopathy has both research and treatment implications. First, it remains to be seen whether the underlying mechanisms responsible for the neuropsychological deficits are due to hepatocellular dysfunction per se or to one of its consequences, such as portal-systemic shunting. Second, the results obtained illustrate the sensitivity of neuropsychological tests for detecting subtle cerebral dysfunction in individuals who do not present clinical evidence of encephalopathy. Indeed, it has been suggested previously that psychometric methods are the most sensitive techniques for the detection of latent or subclinical hepatic encephalopathy (3).

Even more important, the findings of this investigation indicate that neuropsychiatric studies provide information that is not otherwise obtainable, and can be applied to the psychosocial rehabilitation of the patients, such as for the early detection and treatment of hepatic encephalopathy. Hence, quantitative neuropsychological measurement, used as an ancillary diagnostic procedure, might assist either in preventing progressive encephalopathic deterioration or in delaying its development in such patients by demonstrating the need for specific medical therapies before the acquisition of permanent or irreversible brain injury.

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