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Review Article

Cognition in liver disease

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Abstract: *Background:* Cognitive dysfunction has been observed in a range of liver diseases including chronic hepatitis C virus , alcoholic liver disease, primary biliary cirrhosis and Wilson's disease. Such dysfunction may range from mild cognitive changes to overt hepatic encephalopathy, and represents a significant complication of liver disease that may negatively impact the patient's quality of life, and normal activities of daily living (e.g., driving). *Method:* This article reviews the published evidence relating to cognitive dysfunction in liver disease. *Outcome:* Issues of definition, diagnosis, epidemiology, aetiology, treatment and outcome are discussed. Particular attention is devoted to identifying the mild cognitive changes that occur in liver diseases of different aetiology.

Alexander Collie
Centre for Neuroscience, The University of Melbourne, Parkville, Vic., Australia

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Dr. Alex Collie, PhD,
Vic., Australia.
Tel: +613 9664 1300
Fax: +613 9664 1301
e-mail: acollie@unimelb.edu.au

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It is now acknowledged that abnormalities in cognitive function are a common complication of liver disease (1, 2). Individuals with both chronic liver disease and acute liver failure may demonstrate cognitive impairments when compared with healthy, matched individuals, including impairments in memory, attention and psychomotor function (2–5). Such impairment has been associated with significant deterioration in quality of life (6). In many cases, mild cognitive dysfunction leads to overt hepatic encephalopathy (HE), the onset of which precedes death in many patients (7). Early identification of the cognitive manifestations of liver disease is important for both patient monitoring and timing of treatment, and it is now recognised that cognitive assessment may provide useful outcome measures in clinical trials (8). Within this context, there is a need to identify those aspects of cognition that are affected in liver diseases of different aetiology, and also to characterise the cognitive response to common medical and surgical interventions in liver disease.

Definition

The spectrum of neurological abnormalities occurring in liver disease can range from subtle changes in attention and concentration (9) to gross impairments leading to death (e.g., brain oedema; (10)). The term HE is often used to describe these neuropsychiatric changes (8). In its mildest form, HE is termed subclinical hepatic encephalopathy (SHE) or minimal encephalopathy, and is characterised by normal mental and neurologic status accompanied by subtle cognitive dysfunction evident upon neuropsychological or neurophysiological testing (8, 9). This review is primarily concerned with describing the mild cognitive changes occurring in liver disease; however, this discussion is undertaken with reference to studies of HE where required.

Diagnosis

Diagnostic criteria for both HE and SHE have been proposed. Overt HE is a relatively well-characterised clinical syndrome with clear diagnostic guidelines (8), requiring the exclusion of other known causes of brain disease. Despite the interest in SHE as a clinical entity and the increasing volume of research undertaken in this area, there remains no uniformly accepted diagnostic criteria for SHE. For example, one study required that impairment be observed on any one of four outcome measures (11) while another required that performance be impaired on at least two of nine neuropsychological tests (12). A recent consensus statement proposed a 'minimum' test battery for diagnosis, including at least two of five recommended neuropsychological tests (8); however, little guidance was provided regarding interpretation of these test scores. Perhaps the most often used criteria requires that performance greater than two standard deviations below a normal mean be evident on two or more neuropsychological tests (9). However, the statistical probability of meeting this criteria

varies greatly depending on the total number of tests administered (13).

To confound matters further, the tests used to classify SHE have varied widely between studies. Some investigators base their diagnosis on the result of neuropsychological testing alone (9, 12, 14), while others consider the results of neurophysiological and neuropsychological testing concurrently (15–17). Further, there is often no clear rationale for the use of particular tests, and several studies have employed neuropsychological test batteries assessing a limited number of cognitive domains (for discussion see (14)). Many clinical studies incorporate the Number Connection Test (18), and a recent consensus statement proposed a minimal test battery incorporating this test (8).

Epidemiology

Inconsistencies in the diagnostic criteria and methods between studies have contributed to wide variations in the reported prevalence of cognitive dysfunction in liver disease. These inconsistencies make accurate estimation of the prevalence and incidence of such dysfunction difficult. SHE has been reported to occur in anywhere from 30% to 84% (9, 19, 20) of patients with liver disease. In perhaps the largest study to date, SHE was observed in 62.4% of patients (12). In chronic hepatitis C virus (HCV), Hilsabeck et al. (21) found that the rate of cognitive dysfunction varied between 0% and 82% depending upon the neuropsychological tasks used to identify impairment. In North America alone, it has been estimated that 1.5–2 million people may have cognitive impairment associated with liver disease (9). Consensus regarding the best diagnostic approach is required before accurate epidemiological estimates are possible.

Current status of clinical studies

Numerous studies have now sought to investigate neuropsychological outcome in individuals characterised according to clinical stage of disease or disease aetiology. This study design allows the determination of predictors of cognitive impairment (e.g., disease stage), as well as the analysis of clinical signs and symptoms that may covary with cognitive impairment (e.g., fatigue, sleep disturbance, liver biochemistry).

In general, the performance of patients with liver disease and those who have undergone liver transplant is found to be worse than that of healthy matched controls across a range of cognitive tests (2). Further, patients with more severe disease (Child–Pugh Stage C) display greater cognitive deficits than patients with less severe disease on tests of immediate memory and processing speed (2). These findings suggest that patients with end-stage disease may require extra support with daily activities and health-care decision making.

The use of cognitive tests as outcome measures also allows the identification of specific 'patterns' of cognitive impairment in patients with liver disease. This information could then be usefully used to inform the development of test batteries for the diagnosis of SHE. For example, McCrea and colleagues (14) observed a relatively selective dysfunction of attention and motor skills in a cirrhotic group, in the absence of any impairments in general intellect, memory, language or visuospatial skills. These findings, when considered in conjunction with results from other neurological, neuroimaging and physiological studies, led the authors to conclude that cognitive dysfunction in liver disease may be as a result of changes in basal ganglia function. Other authors have observed consistent results (4). Such neuroscientific models may further our understanding of the brains involvement in liver disease.

Studies where group classification is based on disease severity typically fail to differentiate between aetiologies (2, 12, 15). However, a number of studies report cognitive impairment in patients with liver disease of specific aetiology. Most research in this area has focused on patients with HCV, Wilson's disease (WD) and ALD, however other aetiologies have also been investigated (e.g., primary biliary cirrhosis (PBC)).

Viral Hepatitis

There are few direct investigations of cognition in viral hepatitis. Five peer-reviewed studies, all published within the past 3 years, have specifically investigated cognition in HCV (21–25, 26). One striking feature of the research conducted to date is the methodological inconsistencies. For example, only three studies employed comparison groups, and the characteristics of these comparison groups were different between studies (23–25). The neuropsychological outcome measures employed varied widely between studies, ensuring that there is as yet no consistent 'profile' of cognitive dysfunction in HCV. Although these methodological differences make generalisation of findings difficult, a brief summary of the most notable outcomes in HCV is warranted. One common finding is that greater disease severity is associated with greater cognitive dysfunction (26). Further, patients with HCV appear to be impaired to patients with 'cleared' HCV (24). Hilsabeck et al. (21) observed that performance

of patients with HCV did not differ from that of patients with other forms of chronic liver disease. Similarly, patients with HCV display psychomotor impairment equivalent to that observed in patients with HIV seropositive patients with and without concurrent HCV infection (25). Although no study has directly compared HCV with normal healthy individuals, findings from studies of liver disease with mixed aetiology (2, 14) suggest that individuals with HCV have significantly impaired cognition relative to healthy individuals.

There is substantial evidence that hepatitis B virus (HBV) is associated with changes in quality of life and psychological variables (e.g., depression, anxiety) (27) suggesting that there may well be a cognitive impairment in these patients. However, to the author's knowledge, no published studies have directly addressed the issue of cognition in HBV.

Alcoholic liver disease (ALD)

There is a large literature demonstrating an association between chronic alcoholism and cognitive dysfunction (28–31). Cognitive impairments observed in chronic alcoholics without liver disease are commonly thought to encompass executive functions including abstraction, planning, problem solving and working memory (29), while patients with the neurodegenerative Wernicke–Korsakoff's disease typically display impairments in the formation and retrieval of new memory (32, 33). Despite the large number of neuroscientific studies of alcoholism, there have been relatively few studies specifically investigating the contribution of liver disease to the spectrum of cognitive changes observed in alcoholics (34–38). Several authors have hypothesised that the cerebral and hepatic consequences of alcoholism may combine to produce more severe cognitive dysfunction in ALD patients than in non-ALD patients (34, 37, 39). However, and perhaps surprisingly, a consistent finding in the literature has been that ALD and non-ALD patients display equivalent levels of dysfunction on tests of learning and memory, simple and complex attention, psychomotor function and general intellectual ability (34, 37).

Wilson's disease

Neuropsychiatric symptoms are a hallmark of WD, with clinical presentation in adulthood including personality changes and neurological signs such as tremor and dystonia (40). Symptomatic WD patients display mild but clearly significant impairments in many cognitive functions compared with both asymptomatic WD patients and controls (41). Most severely affected are performance on tests of attention and motor speed. A further analysis of symptomatic WD patients with MRI evidence of selective basal ganglia pathology ($N = 19$) and WD patients with diffuse pathology ($N = 31$) found equivalent levels of impairment on all but a few tests (of attention, comprehension and visuo-motor ability), suggesting that subcortical pathology alone is sufficient to cause cognitive impairment in WD. Consistent with these findings, an earlier study observed that slowed motor speed may underlie the broader cognitive dysfunctions observed in WD (42). However, this has been challenged by other authors (43).

Cholestatic liver disease

There is a small literature directly assessing cognition in cholestatic liver disease, specifically PBC and primary sclerosing cholangitis (PSC). A series of studies by Tarter et al. (44, 45) form the foundation of our understanding of cognition in these diseases. One study observed that a greater proportion of individuals with either PBC or PSC were impaired on tests of attention, concentration and psychomotor function relative to a control group of Crohn's disease patients (44). Another study compared 14 PBC patients to 10 PBC patients with co-existent Sjogren's syndrome and 10 normal controls (45). While both PBC groups displayed significant impairments predominantly on tests of attention, psychomotor function and perceptual speed, these impairments were significantly more severe in patients with PBC and co-existent Sjogren's syndrome. Patients with PBC also display more severely impaired performance on a test of general cognitive function than matched patients with rheumatoid arthritis (46).

Other liver diseases

Other forms of liver disease are also associated with deterioration in quality of life, fatigue and depression, including haemochromatosis (47) and autoimmune hepatitis, suggesting that cognition may also be affected. However, as with HBV, there is currently no direct evidence of cognitive dysfunction in these diseases.

Comparative studies

An important issue that has received very little attention is the extent to which the nature and magnitude of cognitive dysfunction varies between types of liver disease. Review of the literature reveals a single study that has addressed this issue (44). This study compared PBC/PSC with

ALD and a group of patients with postnecrotic cirrhosis resulting from viral hepatitis. All groups displayed cognitive impairment relative to a control group with Crohn's disease. A greater proportion of ALD patients were impaired on tests of learning/memory and psychomotor function than other groups. Further studies of this type will allow more accurate identification of the brain regions differentially involved in these liver diseases, and perhaps lead to more appropriately designed cognitive test batteries.

Aetiology

In overt HE, cognitive and behavioural changes are thought to result from alterations in neurotransmission caused by the entry of nitrogenous substances (e.g., ammonia) into the brain tissue via the arterial circulation (48). In patients with mild cognitive dysfunction, the genesis of cognitive alterations is less well established. Two potential causes have been proposed.

First, it is possible that cognitive abnormalities result from pathogenic processes such as those occurring in overt HE. That is, these diseases may indirectly effect brain function, resulting in cognitive impairment. This is certainly the case in WD, in which impaired copper metabolism leads to its accumulation in the brain. Radiological and clinical evidence suggests that copper accumulation in WD occurs mainly in the basal ganglia; however, other CNS areas may also be affected (49–51). The pattern of cognitive dysfunction in WD is consistent with these radiological findings (41, 42, 52). Forton and colleagues (22, 53) have proposed a biological basis for HCV-related cognitive dysfunction, based on magnetic resonance spectroscopy evidence of cerebral metabolite abnormalities in the basal ganglia and white matter. In general, the pattern of cognitive dysfunction in liver disease, commonly encompassing both memory and psychomotor function, suggests the involvement of both cortical and subcortical areas.

The alternative, non-biological, explanation is that the common symptoms of these diseases (ie., fatigue, depression, impaired quality of life) cause a corresponding functional cognitive disturbance. For example, the most common symptom of HCV is fatigue (54), and HCV patients also report psychiatric symptoms including depression and anxiety (55, 56), and poor quality of life (57, 58). Chronic fatigue is one of the most common and debilitating symptoms of cholestatic liver disease, affecting up to 68% of patients (59, 60). The reversible and seemingly transient nature of cognitive impairment in liver disease appears to support this hypothesis. Further research is required to determine the extent to which these biological and psychological explanations interact in individual diseases.

Treatment

Mild cognitive dysfunction may be a precursor to overt HE, the development of which carries a poor prognosis, with survival 1-year postdiagnosis of approximately 40% (7). Identification and treatment of individuals at risk for conversion to HE is therefore important in preventing death among cirrhotic patients. As described in current best practice guidelines (48), there are a number of treatment options for patients with overt HE, including dietary management, reduction of nitrogenous load from the gut, and administration of drugs that affect neurotransmission. In patients without overt HE, there appears to be a strong association between the severity of cognitive dysfunction and the severity of liver disease (46). Patients with better liver function have mild levels of cognitive dysfunction, demonstrate abnormality on fewer tests, are likely to recover from cognitive dysfunction and are less likely to convert to overt HE than patients with worse liver function as rated by Child's scores (12). Thus, early identification and effective management of the liver disease will, to some extent, result in effective management of any associated cognitive dysfunction. There are exceptions to this general rule. For example, treatment of chronic hepatitis with interferon may result in the onset of neuropsychiatric disorders (eg., depression) in many patients (61, 62). Given the known association between such disorders and cognitive impairment, it is likely that interferon therapy will also result in impaired cognition in these patients. Co-administration of anti-depressants during interferon treatment results in a lower incidence of depression (63, 64), and may also result in improved cognition in this patient group.

Because the natural history of mild cognitive dysfunction in liver disease remains largely unknown, there have been few well-controlled studies of specific treatments for such dysfunction. A number of therapies have been shown to improve cognition in liver disease, including lactulose treatment (12, 65, 66), dietary protein manipulation (67) and oral supplementation with branched chain amino acids (68, 69). For example, Watanabe and colleagues (66) observed that SHE disappeared in 10 of 20 cirrhotic patients after 8 weeks of lactulose treatment, whereas SHE resolved in only one of 14 untreated patients during

the same period. Despite these findings, there is currently no consensus regarding the most practical and effective treatment strategy for cognitive dysfunction in liver disease patients without overt HE (12). Aside from pharmacological treatment, it is proposed that management of cognitively impaired patients should incorporate the provision of supportive care services and serial evaluation of cognition.

Outcome

There is little doubt that the cognitive changes in liver disease are associated with serious functional consequences for patients, including decreased ability to perform normal day-to-day tasks such as driving (70) and operating machinery (71), as well as disruptions to the sleep–wake cycle (72) and poorer overall quality of life (6). Subtle cognitive dysfunction may also precede the development of overt HE, with this transition occurring within 6–24 months of diagnosis in the majority of patients (59%) (15). However, other studies have reported that a proportion ($\sim$ 10%) of patients with SHE recover normal cognitive function within a 6-month period (12).

In general, liver transplantation results in improved cognitive function for most liver disease patients. While numerous studies have now reported that cognition improves from pretransplant levels (2, 73–75), others have demonstrated that very subtle impairments persist for at least 10 years posttransplant (76). Patients with ALD who undergo liver transplantation typically display only partial recovery of cognitive function, with persistent memory impairments observed in one study (75). This is in contrast to similar studies in patients with other forms of liver disease who display uniform improvement in cognition (73, 74). These findings raise the possibility that the lasting memory impairments in ALD may be as a result of alcohol-related neurotoxicity, but that other cognitive impairments are caused by a reversible HE. In PBC, one small study observed normal levels of cognition after liver transplantation in seven patients (77). In WD, the role of liver transplantation in treating the cognitive and neurological manifestations remains unclear (78, 79), as does the association between copper toxicity and cognition (80); however, significant improvement in cognitive status has been observed with penicillamine treatment (81).

Summary and conclusions

The past two decades have seen substantial advances in our understanding of the effects of liver disease on cognition. The most common impairments observed are in the cognitive domains of attention, memory and psychomotor function. Studies of specific aetiologies reveal various patterns of dysfunction. The cognitive impairment in WD appears to result from copper accumulation in the basal ganglia. Despite this, patients with WD may display a variety of impairments encompassing attention, memory, language and executive functions, suggesting some level of cortical involvement. In contrast to a common hypothesis, patients with ALD display equivalent impairments to patients with liver disease of other aetiology. However, the memory impairment in ALD does not resolve after liver transplantation. Preliminary findings from studies of HCV and PBC suggest that a range of cognitive functions may be impaired in these patient groups. One common finding is that greater cognitive impairments are observed in individuals with more severe disease. To date, a single study has compared cognitive function in patients with liver disease of different aetiologies.

Lack of standard comparison groups renders comparison of research findings difficult. The dysfunction observed in these studies is typically mild in nature, with patients often observed to perform at the low end of normal limits. Many neuropsychological tests are designed for the detection of gross changes in cognition (82), and therefore may not be applicable in these populations. Selection of tests appropriate for detecting subtle cognitive changes is important in future research, and also for the identification of SHE. Studies of HE suggest that this well-defined clinical entity occurs relatively commonly in patients with liver disease. SHE is less well defined, with no consistent diagnostic criteria or methodology yet evident. The prevalence of SHE among patients with liver disease is poorly characterised, as are the clinical consequences of SHE. Surprisingly, there have been no serial investigations of cognition in liver disease. As a consequence, our understanding of the natural history of cognitive dysfunction in this diverse patient group is poor, as is our ability to evaluate the effectiveness of treatments to alleviate such dysfunction.

Both biological and psychological explanations for the cognitive dysfunction in liver disease have been proposed. The incidence of dysfunction among different liver diseases is poorly characterised, as is the association between cognitive changes and quality of life. While liver transplantation appears to alleviate cognitive dysfunction in studies of mixed aetiology, few studies have investigated posttransplantation cognitive function in specific patient groups.

Further prospective, longitudinal studies combining cognitive, psychological, radiological and physiological methods are required to identify whether specific brain systems are implicated in liver diseases, to identify the associations between psychological variables (e.g., fatigue, depression, anxiety) and cognitive outcome, and also to examine the changes in cognition that occur throughout the disease process. These studies must be conducted in liver disease of specific aetiology. Such research will provide a firm basis for understanding the central nervous system involvement in liver disease and for development of evidence-based clinical criteria for SHE.

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