Neuropsychological aspects of liver disease and its treatment

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Suggested Running Head:
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Abstract

Liver disease can lead to serious impairment in cognitive functioning, through the development of a condition known as hepatic encephalopathy (HE). While gross impairment is clinically obvious, milder variants of the condition may escape detection at bedside examination and yet may have a significant impact on day-to-day activities. In this brief review article, the neuropsychology of liver disease is examined, focusing on nature, aetiology and significance. The possible contributory role of endogenous benzodiazepines in HE is described, as is the evidence regarding the effect of benzodiazepine antagonism on cognitive functioning in HE. The functional localisation of HE is briefly reviewed, as is the use of neuropsychological measures to evaluate treatment efficacy, e.g. following shunt procedures or liver transplantation. Finally, living donor liver transplantation is described, and the case is made for rigorous longitudinal neuropsychological evaluation of potential donors and recipients.

Key words

Hepatic encephalopathy, psychology, cognition, memory, psychomotor
Introduction

Neuropsychology is the study of brain-behaviour relationships [1]. Historically, neuropsychology utilised the classical lesion-based approach, i.e. relating focal brain damage to observed changes in behaviour and cognitive functioning. However, many clinical conditions lead to impairments in cognitive functioning that cannot be attributed to a focal brain lesion, and liver disease is one of these conditions. The liver plays a key role in removing toxins from the blood, including substances that are neurotoxic. When the liver becomes scarred and cirrhotic, some of the blood entering the liver via the portal vein cannot penetrate the diseased liver. As a result the blood that has not been processed by the liver is diverted into the general circulation. This is known as portal-systemic shunting. As the blood that has bypassed the liver has not had toxins removed, the level of these toxins in the systemic circulation increases and the condition of Hepatic Encephalopathy (HE) can arise [2]. HE develops when brain function is impaired by the presence of toxins in the bloodstream (absorbed from the colon) which are normally removed or detoxified by the liver. Symptoms include drowsiness, confusion, cognitive impairment and coma. HE occurs only with significant liver dysfunction and has the potential for full reversibility [3-5]. HE has traditionally been graded using the Parsons-Smith criteria, a 5 point rating scale ranging from Grade 0 (no abnormality detected) to Grade 4 (indicating coma) where mental state is not testable [6]. The overt form of HE is clinically obvious but recently there has been increasing interest in the milder end of the HE continuum. This has been called sub-clinical, latent or mild HE. It has been estimated that 1.5-2 million people in North America alone may have cognitive impairment associated with liver disease [7] and the prevalence of subclinical HE in cirrhosis has been reported to range from 30-84% [8]. This wide variation in estimated prevalence is
because there is no agreement as to what constitutes subclinical HE. The number and type of cognitive abnormalities that need to be present before a diagnosis of subclinical HE can be made differs throughout the literature. It is consequently impossible to produce accurate figures regarding prevalence. [9]. A consensus statement recently proposed a minimal cognitive test battery for the assessment of HE [8], However, a disadvantage to this test battery is the inclusion of the number connection test [10] which has been shown in several studies to be insensitive to mild HE [11, 12]. Nevertheless, there is consistent evidence of psychomotor slowing and memory impairment in subclinical HE. Oritz and colleagues have recently reported data suggesting that the learning and memory impairment is secondary to an attentional deficit caused by HE [13]. Subclinical HE may be present in the majority of the “healthy” ambulant, non-clinically encephalopathic cirrhotic population, for example, Gitlen et al. [7] and Moore et al. [11] both reported that over 70% of cirrhotic patients demonstrated impairment in two or more of the cognitive tests employed, compared with 10% or less of those in their control groups.

Significance of latent hepatic encephalopathy?

If subtle impairment of psychomotor speed and memory is found in the majority of patients with liver cirrhosis, does it matter? The relationship between speed-dependent visuo-spatial abilities and everyday activities such as driving is obvious. Schomerus et al. [14] estimated that 60% of their patients with subclinical HE were unfit to drive and a further 25% were of dubious driving ability. Dunk and Moore [15] argued that such patients who drive or operate heavy machinery may put themselves and others at risk. In a more recent study, it was reported that 44% of patients with subclinical hepatic encephalopathy were unfit to drive and that routine
testing of cirrhotic patients for ability to drive could have a major impact on motor vehicle accident rates [16]. Many of the studies in this area have been limited by the use of driving simulations. Wein et al. recently utilized a standardized on-road driving test and reported significantly impaired driving performance in many patients with subclinical hepatic encephalopathy. During the assessments the instructor had to intervene in the driving of over one-third of the patients with subclinical HE in order to avoid an accident, significantly more than in cirrhotic patients without HE or matched controls. The authors concluded that patients with liver cirrhosis should be tested for mild hepatic encephalopathy and informed in the case of abnormal test results [17].

The identification of mild hepatic encephalopathy is also important for prognosis, as approximately 50% of patients with subclinical HE develop full clinical encephalopathy within 4-24 months [18] [19]. As Davies et al point out, failure to detect mild hepatic encephalopathy can lead to the patient being at increased risk of becoming clinically encephalopathic, with an associated reduction in life quality [20].

*Aetiology of Hepatic Encephalopathy (HE)*

As stated above, one of the major functions of the liver is to remove toxins from the blood. HE is thought to develop as a consequence of biochemical disturbance of brain function. Evidence to support this explanation of HE is twofold: (a) it is a reversible phenomenon, and (b) it does not cause marked pathological changes in the brain. Liver failure and portosystemic shunting of blood are two main factors underlying HE and the relative contribution of each varies from patient to patient [3]. We still do not know the exact nature of the biochemical “neurotoxins” that cause HE, but they are thought to be nitrogenous substances produced in the gut, possibly by bacterial action.
These nitrogenous substances are normally metabolised by the healthy liver so that they do not enter the systemic circulation.

Historically, ammonia was considered to be a key factor in the genesis of HE. Ammonia concentrations are raised in the systemic circulation and in the cerebral spinal fluid (CSF). Previous studies have reported that in patients with advanced stages of HE, ammonia levels in the brain may increase more than twenty times normal levels [21]. Ammonia is known to inhibit cellular chloride channels, which contribute to depression of the central nervous system. Ammonia also facilitates the uptake of tryptophan into the brain, which is a substrate for many metabolites, including serotonin. Ammonia also decreases glutamatergic neurotransmission, causing neurodepression [3]. Evidence supporting the role of ammonia in the pathogenesis of HE is provided from observations that a syndrome resembling HE is produced by hyperammonoemia in the absence of cirrhosis or portosystemic shunting. In addition, a reduction of circulating ammonia concentrations by treatment with lactulose and antibiotics improves HE, and encephalopathy has been precipitated in patients with cirrhosis by administration of ammoniagenic substances [3]. However, ammonia cannot be the sole factor in HE as; (a) there is often a poor correlation between serum and CFS ammonia levels and the degree of HE, and (b) encephalopathy is sometimes observed in patients who have normal ammonia levels. Other possible explanations for HE include “false neurotransmitters” such as octopamine, amino acids, mercaptans, fatty acids and endogenous benzodiazepines [22].
The role of endogenous benzodiazepines?

Since 1989, a controversy has raged over the possible role that natural benzodiazepine (BZ) like substances may play in the pathogenesis of HE [22]. The natural or endogenous benzodiazepine hypothesis states that HE is the consequence of the accumulation of endogenous benzodiazepine-like substances (“endozepines”) in the brain. It is proposed that these are either derived from the diet, or are produced in the gut by bacteria or fungi. In people with significant cirrhosis, these endozepines are not removed by the liver, and accumulate in the systemic circulation. The endozepines are thought to play a role in the development of HE by simulating the effects of exogenous benzodiazepines (e.g. diazepam) on brain function. Elevated levels of BZs have been found in rats and rabbits in fulminant hepatic failure [23, 24]. In an early human study, Mullen et al. reported greater binding of ligands to BZ receptors in CSF taken from patients with severe HE, and plasma BZ activity was also significantly higher, and correlated with HE severity [25]. This finding was also reported by Basile [26]. Olasma et al. also reported markedly elevated levels of a diazepam like substance in the frontal cortex of patients who had died from fulminant hepatic failure, and the levels were up to 10 times that found in the CSF of non-encephalopathic patients with liver disease [27]. Several studies since then have reported elevations in BZs in patients with HE, however, the overlap between comparison groups is often significant. For example, Hernandez-Avila et al., [28] while finding elevated BZ levels in a group of HE patients, also reported that 20% of cirrhotic patients without HE had elevated BZ levels, and that a third of patients with HE had undetectable BZ levels. They concluded “HE cannot be explained by the presence of these compounds alone” p.221 [28]. An important study was reported by Avallone et al. who compared a large group of patients with cirrhosis with healthy
participants, but they also included a group of BZ consumers (regular users of
diazepam or lorezapam as sedatives) [29]. When detectable, endogenous BZ levels in
the cirrhotic group were comparable with those of the BZ consumers, but the levels
correlated with the degree of liver dysfunction, not the stage of encephalopathy. This
led the authors to conclude that endogenous BZs appear to accumulate in some
patients with cirrhosis during the course of their disease, but that this is not clearly
related to the presence or stage of HE [29].

Reversing HE via BZ receptor antagonism

The inhibitory tone of the BZ-GABA-ergic neurotransmitter system appears to be
increased in HE [22], therefore it was logical to study the effects of drugs interacting
with this system in the treatment of HE. Flumazenil is a competitive BZ receptor
antagonist, and has a high affinity for BZ receptors, rapidly reversing the hypnotic
and sedative effects of BZs following intravenous administration. Early uncontrolled
clinical case-studies, reported encephalopathic patients with cirrhosis waking from
HE coma following flumazenil infusion e.g. [30]. Further uncontrolled group studies
reported significant improvements in 60-70% of patients with HE following
flumazenil infusion [31, 32]. The first randomised controlled-trial of HE using
flumazenil versus placebo randomly allocated 11 patients to flumazenil and 10 to
placebo infusion. Six patients treated with flumazenil showed improved neurological
symptoms whereas no participants in the control group showed improvement [33]. It
is important to make two points about this much-cited study; (a) 56 patients were
excluded from the study because of potential confounders such as multi-organ failure
or prior use of BZs, and (b) blood levels of BZ receptor ligands did not correlate with
response to flumazenil. In a subsequent randomised-controlled trial, Gyr et al
reported a clinically significant immediate response to infusion in 7/28 flumazenil treated patients versus 0/21 in the placebo group, and concluded that a subgroup of patients with HE may benefit from flumazenil administration [34]. Most of the flumazenil studies have tested its efficacy in reversing severe HE, e.g. coma. As stated above, however, mild HE is extremely common, and Gooday et al. [35] conducted a double-blind placebo-controlled cross-over study in patients with sub-clinical HE using a low-dose (0.2mg/kg) flumazenil infusion versus saline, and found that reaction time (particularly cognitive, as opposed to motor speed) was significantly improved in patients and not healthy controls. The authors concluded that endozepines may contribute to the psychomotor slowing that is commonly observed in HE, and they also raised the possibility that endozepines may be implicated in other psychopathological conditions where psychomotor retardation is prominent (e.g. major depression).

A recent Cochrane review of BZ receptor antagonists for HE reviewed 13 randomised trials with a total of 805 patients. All of the trials were double-blind and assessed flumazenil versus placebo. Across studies, flumazenil was found to have a significant beneficial effect on improvement in HE at the end of treatment (risk difference 0.28; 95% CI 0.20 to 0.37, 8 trials), but had no effect on recovery or mortality. Future research needs to determine if treatment with flumazenil leads to sustained improvement or increased recovery and survival. Until this is demonstrated, flumazenil may be considered for patients with HE, but it cannot be recommended for routine clinical use [36].

The endogenous BZ explanation of HE has been a controversial hypothesis. It has been suggested that it may not be the absolute level of BZ that is important, but rather changes in affinities or brain densities of BZ receptors [37].
Many have also argued that any effects attributed to endogenous benzodiazepines are, in fact, the result of (a) dietary origin, or (b) patients taking exogenous benzodiazepines surreptitiously. It has also been suggested that any beneficial effects of flumazenil are likely to be attributable to its activity as an antidote to the BZ medications that are frequently prescribed to cirrhotic patients either as part of an endoscopic evaluation, or as a sedative. It may be that flumazenil reverses the *exogenous* BZ effects in these patients, rather than treating HE itself [2]. In considering such claims, Desarathay & Mullen state: “Some may still consider exogenous ingestion of benzodiazepines to be the major cause of hepatic encephalopathy in cirrhotics and for finding benzodiazepines in their blood. If that were true, then possibly the validity of the results of every study on the pathogenesis of hepatic encephalopathy since 1959, when benzodiazepines became available, would need to be questioned” p.765 [38].

HE is, in all probability, a multifactorial disorder, and while abnormalities of the GABA/BZ complex may play a role in some patients, it is extremely unlikely that endozepines account for all the neuropsychiatric manifestations of the syndrome [35].

*Hepatic Encephalopathy – Cerebral localisation of dysfunction?*

The most common neuropsychological abnormalities in patients with varying degrees of HE is memory impairment and psychomotor slowing [39]. In an early study using cognitive assessment and single photon emission computerised tomography (SPECT), O’Carroll and colleagues compared a group of patients with cirrhosis who were considered by their physicians to be cognitively intact, and compared them with a group of age, gender and IQ matched healthy controls [12]. The cirrhotic group were significantly impaired on all cognitive tests relative to controls, with the exception of
one, the Number Connection Test [10] – which just happens to be one of the tests that is the most widely used for the assessment of cognitive impairment in liver disease!

The SPECT scans revealed bilateral hypermetabolism in the basal ganglia in patients with cirrhosis, and the degree of basal ganglia abnormality correlated with the degree of psychomotor slowing [12]. In the same year, Lockwood and colleagues conducted a similar study using positron emission tomography (PET) scans, and also reported increased regional cerebral blood flow in subcortical regions, particularly the thalamus and caudate [40]. Since then a number of structural brain scanning studies using magnetic resonance imaging (MRI) have confirmed abnormalities in subcortical regions, e.g. the globus pallidus [41]. The degree of abnormality in these regions correlates with the degree of psychomotor impairment [42]. It appears that the abnormal MRI signal from the globus pallidus brain region in patients with cirrhosis may be caused by depositions of manganese. Manganese is usually removed from the body by the hepatobiliary system, but when the liver is damaged the system does not function efficiently and the metal enters the brain and is deposited in the basal ganglia region [2]. Butterworth and colleagues reported manganese levels seven times higher than normal in the globus pallidus region of patients with cirrhosis [43]. Taken together, this evidence suggests that manganese deposited in the basal ganglia may contribute to the psychomotor symptoms of HE.

*Using Neuropsychological Instruments to measure treatment response*

The development of neuropsychological measures over the past century has led to the accumulation of a vast number of cognitive tests which permit the valid and reliable quantification of various aspects of cognitive functioning. This is particularly important when one is trying to determine subtle effects of interventions. As stated in
the introduction, the traditional approach to measuring HE was by using the Parsons – Smith criteria, which ranges from normal to coma in 5 stages – (not the most subtle of gradations!). When clinical changes are not gross, they can be missed by bedside examination, and it has been proposed that the majority of patients with mild, but significant HE, are not detected routinely. A major problem in cirrhosis is that the scarring leads to difficulty in the blood passing through the liver, and portal hypertension results. This pressure can lead to the development of oesophageal varices (large swollen veins around the oesophagus). Under consistent portal hypertension, these varices can rupture and bleed, and severe variceal bleeding is often fatal. Portosystemic shunt surgery used to be the treatment of choice, where a shunt was inserted that effectively enabled blood to bypass the liver, thus rapidly reducing portal hypertension. However, as the liver was effectively taken out of the circulatory loop, toxins continued to accumulate in the systemic circulation and HE often developed. In addition, the mortality associated with the procedure was high [44]. A more conservative alternative procedure was developed – transjugular intrahepatic portoystemic stent shunting (TIPPS). TIPPS involves a small stent being placed between the portal vein and the hepatic vein in the liver to provide a portosystemic shunt to reduce portal pressure. Successful shunt placement thus reduces portal hypertension and prevents variceal bleeding. When TIPPS was introduced, a significant concern was whether the shunt would also lead to the gradual development of HE in recipients. Rather than wait to see if full-blown HE and coma developed, neuropsychological assessment (e.g. of psychomotor speed and memory) has been conducted pre and post TIPPS, to see if the development of encephalopathy could be detected at an early stage. Jalan et al. compared 29 TIPSS patients with healthy participants, and also included a group of cirrhotic patients who were not
TIPPS candidates. All participants were serially assessed using matched parallel versions of the neuropsychological tests in order to counter the effects of learning/practice effects [45]. Only 1 of the TIPPS patients developed HE over the 9 month study period. The study demonstrated the potential usefulness of repeated neuropsychological assessment, using sensitive measures with parallel versions, when evaluating interventions in liver disease.

Liver Transplantation

Perhaps the most radical treatment for liver disease is liver transplantation [46]. Traditionally this involves the harvesting of a liver from a cadaver and transplanting the organ into the recipient. This is either an elective procedure e.g. following evaluation and a period on a waiting list for patients with chronic liver disease, or is an acute response to fulminant hepatic failure, e.g. following paracetamol overdose. Liver transplantation has become a very well established procedure, with 5 year survival rates of around 75% commonly reported [47]. It is clearly a life-saving intervention for patients in liver failure. However, increasing attention is being paid to evaluating psychological and social outcome in recipients, e.g. quality of life and cognitive functioning as key outcomes [48-51].

For a three-year period (1996-1999) all patients who were evaluated for possible liver transplantation in Scotland underwent detailed psychological assessment by a trained psychologist [52]. The assessment covered the domains of mood, fatigue, cognitive functioning and quality of life (QoL). All liver transplant recipients were assessed pre, and serially post transplant, and their performance was compared with two comparison groups; (a) healthy participants (hospital staff) and (b) patients with chronic liver disease who were not transplant candidates. Cognitive impairment in
transplant candidates was common, e.g. of 164 candidates assessed, only 21% performed within the normal memory range on the Rivermead Behavioural Memory Test [53], thus approximately 80% of transplant candidates had varying degrees of memory impairment. Also 45-60% of candidates had evidence of significant psychomotor slowing. In this national sample of liver transplant candidates, memory impairment and psychomotor slowing were therefore the norm. This raises two issues; (a) the impact of this degree of cognitive impairment on the ability to give informed consent for a potentially life threatening procedure, and (b) the potential reversibility of this cognitive impairment following liver transplant. When tested one year later, transplanted patients showed significant improvement on most psychological domains relative to both healthy comparison participants and patients with chronic liver disease who were not transplant candidates. However, it is important to note that while the liver transplant recipients showed highly significant improvements in memory and psychomotor speed at 1 year post-transplant, their performance did not improve to the level of healthy participants. The liver transplant recipients’ mean scores for memory, simple and choice reaction time fell at a level similar to the control participants who had chronic liver disease, but were not transplant candidates – (see Figures 1& 2 for reaction time data). These results suggest that while marked neuropsychological recovery is observed at 1 year post-transplant, this recovery is incomplete, i.e. liver transplantation does not fully “normalise” cognitive performance, and that some residual degree of cognitive impairment remains [52]. It is often assumed that any cognitive impairment that is observed in liver disease is attributable to the neurotoxic effects of alcohol, however, the majority of participants in this study had a non-alcoholic aetiology (the most common diagnosis was primary biliary cirrhosis). Furthermore, most studies do not
report a differential outcome when comparing liver transplant for patients with alcohol versus a non-alcohol related aetiology. We do not know how, or if, the residual cognitive impairment we observed impacts upon day-to-day functioning, e.g. driving ability. Further work is also required in order to test whether continuing recovery accrues over time. This type of work highlights the importance of the sensitive and reliable assessment of neuropsychological status in determining the full impact of surgical and medical interventions in liver disease.

Living Donor Liver Transplantation

The above section described liver transplantation with organs retrieved from individuals who had died. However, as a result of low donation rates, patients can often face a long wait for a new liver. Many patients consequently become too ill to go through with the transplant operation, or die before a suitable organ is found. The lack of organs from cadaveric donors is a problem found in every transplant unit throughout the UK and beyond. Three out of four GPs believe that the UK should introduce an “opt-out” organ donor scheme. Within this scheme, organs from those who have died may automatically be removed and used to save the lives of those in need of transplants. This would happen unless the donor or their family specifies that organs may not be used in this way. The move, if adopted in the UK as it is in some other countries, could dramatically reduce the death rate among those currently awaiting transplantation. However, proposals for an “opt-out” scheme have repeatedly been rejected in the UK, and many patients continue to die while awaiting an organ transplant. Currently in Scotland, approximately one patient on the elective liver transplantation waiting list dies every month. In an attempt to improve the situation, a radical alternative to donation from cadaveric donors has been developed. This is
known as Living Donor Liver Transplantation (LDLT), a groundbreaking treatment for serious liver disease. LDLT enables a healthy family member to donate the right lobe of their liver (approximately 60 per cent of the liver mass) to a sick relative. LDLT has been described as “one of the most invasive procedures that could be contemplated for healthy individuals” p.24 [54]. Transplantation from a living donor is made possible through the liver’s unique ability to regenerate once it has been split. This is the case for both the part of the liver transplanted into the recipient and the part that remains in the donor.

LDLT was first developed in Japan where organs from individuals who have died are not used for cultural reasons. Over the past 10 years, other countries such as North America, Asia, France and Germany have started to offer LDLT as an alternative to transplantation from non-heart beating donors. In 2003, LDLT accounted for 5% of all liver transplants performed in the USA. Although LDLT may seem like an ideal solution to the waiting list problem this “lifeline” comes at a cost. The healthy donor has to go through a major operation with no physical benefit to him or herself. The risk of death for the donor is considerable (originally estimated to be between 0.5 and 1 per cent [55] and is far higher than the risk of death found when a person decides to donate one of their kidneys to a relative (0.03 per cent). In addition, the risk of medical complications arising from the operation has been estimated at around 50 per cent [55]. However, as each centre that has developed an LDLT programme has had their own individual reporting methods, it is difficult to establish exact morbidity figures, e.g. a complication in one centre may not have been noted as such in another. The few quality of life studies that have been conducted following LDLT generally report positive outcomes (e.g. [56]). However, approximately one third of donors felt that recovery took longer than expected, and a third to one half reported the pain as
worse than expected. In addition, 30-40% of donors reported that the surgical scar was worse than expected [54]. Complaints of throbbing, itching and numbness around the wound are relatively common [57]. In one study, “easily felt distress and anger” was reported by over 50% of donors following the LDLT procedure [57]. A systematic review of LDLT outcomes has recently been published where 214 studies which provided information on donor outcomes were analysed [54]. In this review, it is estimated that approximately 6,000 LDLT procedures have been performed worldwide, with 12 -13 donor deaths. The calculated mortality for right lobe donors to adult recipients was 0.23 to 0.5%, with a median morbidity rate of 16%. The most commonly reported morbidities were biliary complications and infections [54].

The authors of the recent systematic review state: “Although patient numbers are too small to determine clear patterns of causes of death after donation there is some indication that right lobe donors may not be left with sufficient liver reserve” [54] p.28. An adult recipient needs the large right lobe of the donor’s liver to be transplanted into them, leaving the donor with the smaller left lobe of their liver. The liver starts to re-grow immediately after the transplant operation and regenerates to about double the size of the remnant liver within several months, reaching a median 89% of the original liver size [54, 58]. It has still to be determined how this period of reduced liver mass (and potential hepatic insufficiency) in the months following LDLT impacts upon the cognitive status and functional capacity of the recovering donor. For example, is 40% of the liver sufficient to remove toxins from the blood adequately, or is it possible that in the months following the operation, toxins accumulate in the systemic circulation, and a mild hepatic encephalopathic state develops, which gradually resolves over time as the liver regenerates in the donor?
There is a paucity of evidence regarding such psychological outcomes following LDLT, as Caplan states “the pursuit of living donors as a source of lobes of liver for transplant has proceeded in something of a data vacuum” p.494 [59]. Further longitudinal research, using appropriately sensitive neuropsychological measures is urgently required in order to address this important issue [60].

References


Figure 1
Changes in Simple Reaction Time by Group
Figure 2
Changes in Choice Reaction Time by Group

Liver Transplant
Liver Patient Control
Healthy Participant