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ORIGINAL PAPER

Hepatitis C virus infection and the brain

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Abstract There is growing evidence that hepatitis C virus (HCV)-infection may affect the brain. About half of the HCV-infected patients complain of chronic fatigue irrespective of their stage of liver disease or virus replication rate. Even after successful antiviral therapy fatigue persists in about one third of the patients. Many patients, in addition, report of deficits in attention, concentration and memory, some also of depression. Psychometric testing revealed deficits in attention and verbal learning ability as characteristic for HCV-afflicted patients with normal liver function. Magnetic resonance spectroscopic studies showed alterations of the cerebral choline, N-acetyl-aspartate, and creatine content in the basal ganglia, white matter and frontal cortex, respectively. Recently, pathologic cerebral serotonin and dopamine transporter binding and regional alterations of the cerebral glucose utilisation compatible with alterations of the dopaminergic attentional system were observed. Several studies detected HCV in brain samples or cerebro-spinal fluid. Interestingly, viral sequences in the brain often differed from those in the liver, but were closely related to those found in lymphoid tissue. Therefore, the Trojan horse hypothesis emerged: HCV-infected mononuclear blood cells enter the brain, enabling the virus to reside within the brain (probably in microglia) and to infect brain cells, especially astrocytes.

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A few years ago a direct relationship between hepatitis C virus (HCV) infection and brain dysfunction was considered improbable. While it was common clinical knowledge that part of the HCV-infected patients complained of compromising fatigue, mental and physical exhaustion or "brain fog" (Forton et al. 2006) these symptoms were related to liver disease per se but considered to be unrelated to the cause of liver disease. HCV infection was feared as one of the major causes of liver cirrhosis and hepatocellular carcinoma. First estimations expected about 30% of the HCV-infected patients to develop liver cirrhosis. Meanwhile it has been shown that the risk varies depending on several co-factors such as age at the time of infection, sex, co-morbidities, route of infection, or alcohol consumption, for example, and that the frequency of cirrhosis ranges from less than 1% up to 25% depending on these co-factors (Wiese et al. 2000, 2005; Seeff 2002; Kenny-Walsh 1999). On the other hand about 50% of the patients complain of neuro-psychiatric symptoms and a reduction of their health related quality of life irrespective of their individual grade of liver disease. This paper aims to give an overview upon the current knowledge about the impact of HCV exposure on brain function.

HCV and quality of life

It is consensus that HCV-infection impairs health related quality of life (HRQL). Whether this is due to physiological or psychological effects, however, remains controversial. Several studies have been performed aiming to answer this question. In 1998 Foster et al. reported their survey on health related quality of life in 72 hepatitis C patients without liver cirrhosis compared to 30 subjects with chronic hepatitis B and 17 healthy controls. The hepatitis C patients scored worse in the SF 36—a HRQL-questionnaire—than hepatitis B patients and controls. While HBV-afflicted patients scored less than controls only with regard to "mental health" and "general health perception" the HCV-afflicted patients scored worse than the controls in every subscale of the score. The SF36 score was neither related to the presence or absence of a history of drug abuse, nor to the degree of hepatic inflammation or liver enzyme levels in the blood. In addition it was similar in patients diagnosed by chance and in patients who had undergone medical examination because of clinical symptoms. In 1999 Rodger et al. showed that even subjects who were unaware of their HCV-infection achieved lower quality of life scores than healthy controls.

Recently the Patient Support Group Deutsche Leberhilfe e.V. and the Federal Hepatitis Competence Net in Germany published data on socio-economics and quality of life in German hepatitis B and hepatitis C patients (Niederau et al. 2006, 2007, 2008). Overall 1,500 questionnaires were distributed by clinics, practitioners, and patient support groups to either group. Two hundred fifty-five hepatitis B patients compared to 714 hepatitis C patients returned the completed questionnaires. Health related quality of life was assessed using the SF12. Mental and physical quality of life was reduced in both patient groups compared to a sex- and age-matched general

population ($p<0.001$). In hepatitis B patients both, mental and physical quality of life, was significantly less impaired than in hepatitis C patients ($p<0.001$) although liver disease was more pronounced in the hepatitis B group (percentage of cirrhosis: hepatitis B 28%, hepatitis C: 14%).

Thus, HCV-infection seems to be more prone to HRQOL reduction than HBV-infection. One possible explanation is a frequent affection of the central nervous system in HCV-infection in contrast to HBV-infection.

Indeed there is increasing evidence for CNS-affection in HCV-exposed patients. Data point to a high frequency of fatigue, cognitive dysfunction and mood alterations in these patients combined with alterations in brain metabolism and neurotransmission.

HCV and fatigue

Chronic fatigue is characterized by difficulties to initiate and/or complete wilful actions. It is a frequent symptom of various disorders of the central nervous system (CNS), such as Parkinson's disease or multiple sclerosis. Lesions of the attention or arousal system, especially the ascending reticular activating system, the limbic system and the basal ganglia are regularly associated with chronic fatigue.

Patients with chronic fatigue due to CNS disorders feel continuously physically and mentally exhausted. They complain about deficits in attention, concentration and memory. Some suffer in addition from sleep disturbances, headaches, muscle and joint pain and depression (Chaudhuri and Behan 2004). Strikingly, these are the characteristic complaints also of a majority of the hepatitis C patients with chronic fatigue. According to the most recent survey of the Patient Support Group Deutsche Leberhilfe e.V. and the Federal Hepatitis Competence Net in Germany based on completed questionnaires of 5,837 patients with chronic hepatitis C (Hüppe et al. 2008) 45.6% of the patients feel continuously fatigued. It must be emphasized that only 3% in this patient group had liver cirrhosis.

The German data are consistent with data from Poynard et al. (2002) who found chronic fatigue in 53% of 1,614 patients. Seventeen percent of the patients suffered severe disabling fatigue. The assessment had been done before antiviral therapy was started. Hassoun et al. 2002 assessed the presence and severity of fatigue in 92 hepatitis C patients compared to 116 patients with primary biliary cirrhosis (PBC) and 213 healthy blood donors. Again more than half of the hepatitis C patients (63%) complained of fatigue. The Fatigue Impact Scale Score (FIS) was pathological in more than two thirds of the patients, but the mean FIS score of the PBC group was significantly higher than that of the hepatitis C patients.

Kallman et al. (2007) differentiated between chronic fatigue syndrome and chronic fatigue. Chronic fatigue was defined as fatigue persisting ≥6 months. Chronic fatigue syndrome was diagnosed if in addition to fatigue patients complained of at least four of the chronic fatigue syndrome items such as impairment of short-term memory, sore throat, tender lymph nodes, muscle pain, un-refreshing sleep, joint pain, headaches, malaise lasting for more than 24 h after exertion with these symptoms being present simultaneously for the past 6 months. Seventy one percent of their hepatitis C patients ($n=95$) compared to 25% of the

controls (n=53) complained chronic fatigue. A chronic fatigue syndrome was diagnosed in 27% of the patients and 11% of controls. In both groups chronic fatigue was related to a decrease in HRQL. Neither chronic fatigue nor HRQL were associated with route of transmission, age, or gender. Patients with cirrhosis achieved lower HRQL scores but did not differ from those without cirrhosis with regard to the fatigue scores.

The pathophysiology of chronic fatigue in hepatitis C patients has not yet been clarified. Alteration of serotonergic neurotransmission is suggested as a possible cause. Jones (1999) observed by chance that ondansetron, a 5-hydroxytryptamine-3-receptor antagonist, improved a HCV infected patient's well being by a marked reduction of fatigue and an increase in the patient's psychomotor speed. Piche et al. (2005) performed a randomised, placebo-controlled trial to analyze the effects of ondansetron on fatigue in chronic hepatitis C. They found a 30% improvement of the fatigue scores in the verum group after 15 days, 30 days and 60 days of treatment, while the placebo group showed no persistent significant change of fatigue. Alteration of the serotonergic neurotransmission in chronic hepatitis C has also been suggested by Cozzi et al. (2006) who found decreased serum tryptophan concentrations in HCV-infected patients (n=39), while the concentration in hepatitis B patients (n=10) did not differ from controls (n=40).

HCV and cognition

Hepatitis C patients frequently complain of difficulties in attention, concentration and memory. They report to be unable to grasp things or to take in what people are saying. Several patients stop driving because they feel unable to pay due care and attention to the traffic or because they notice orientation deficits. The frequent reports of a lack of mental clarity or inability to function effectively have led to a number of studies upon cognitive function in patients with hepatitis C, which in fact give evidence for alteration of cognition. To establish a direct relationship between cognitive dysfunction and HCV-infection other possible causes of cognitive impairment must be excluded. Therefore it is necessary to take account especially of minimal hepatic encephalopathy, Hashimoto encephalopathy or the effects of chronic drug abuse, if applicable. In addition the influence of anxiety and depression on psychometric test results has also to be considered.

In 2002 Forton et al. first reported impairments of attention, concentration and psychomotor speed in patients with hepatitis C. They compared the psychometric test results of 27 HCV-RNA-positive patients with histologically proven minimal hepatitis to those of 16 PCR-negative formerly HCV-exposed patients. The cognitive assessment was done using the CDR battery (Cognitive Drug Research computerized assessment system), the Number Connection Tests and the Digit Symbol Substitution Test. The computer battery provides scores for the power of concentration, speed of memory processes, quality of working memory and the ability to sustain attention. The power of concentration and the speed of memory processes were significantly decreased in the HCV-infected patients compared to healthy controls. In contrast the performance of the patients who had cleared the virus was equivalent to the controls.

In addition to the cognitive assessment 19 patients of the HCV-infected group and the whole HCV-cleared group completed the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scales (HADS), a fatigue score and the SF36. The two groups did not differ with regard to fatigue, anxiety score of the HADS and the mental summary score of the SF36, while the PCR-positive patients achieved worse depression scores in the HADS and BDI and a lower physical summary score in the SF36 than the PCR-negative patients. Interestingly the cognitive and affective scores showed no interrelationship.

As in most other studies on this topic about half of the patients in both groups had a history of intravenous drug abuse, and 69% of the PCR-negative patients had cleared the virus after interferon therapy.

We compared the psychometric performance of 30 PCR-positive patients with only mild liver disease to healthy controls (Weissenborn et al. 2004). Half of the patients complained of moderate to severe fatigue, the other half felt unimpaired. Patients with concomitant medical, neurological or psychiatric diseases, drug abuse, interferon therapy or other medication that might impair cerebral function were excluded. In concordance with Forton et al. (2002) we found significant attention deficits in the patients compared to controls, as well as increased anxiety and depression scores and decreased SF36 scores. The moderately to severely fatigued patients were more compromised than the mildly fatigued patients. But even the mildly fatigued patients who felt unimpaired showed attention deficits and slightly increased anxiety and depression scores compared to healthy controls.

McAndrews et al. (2005) confirmed the presence of slight attention deficits and an impairment of verbal learning ability in their study of 37 patients with chronic HCV infection compared to 46 healthy controls. But, they felt the cognitive dysfunction in their patients being of little clinical significance, since out of ten psychometric tests a group difference was only present in the California Verbal Learning Test, and only 13% of the patients achieved pathological test results.

In contrast, Fontana et al. (2005, 2007) reported that 33% of 177 patients who were examined in the HALT-C trial before treatment with peg-interferon and ribavirin had cognitive impairment with alterations in verbal recall and working memory. One third of their patients had liver cirrhosis. Thus, hepatic encephalopathy must be considered as a confounding factor. Alterations in verbal recall and working memory, however, are not the typical cognitive changes of minimal hepatic encephalopathy (Weissenborn et al. 2001). In addition, the authors had shown in their first paper related to cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial (Fontana et al. 2005) that there was no consistent correlation between individual psychometric scores and liver histology or laboratory data such as serum albumin or bilirubin levels.

Up to now, two groups were unable to show cognitive deficits in HCV-infected patients with normal liver function. Juan Cordoba and co-workers examined 40 patients with chronic hepatitis C, 40 patients with compensated HCV-cirrhosis and 40 patients with decompensated HCV-cirrhosis compared to 40 healthy controls (Cordoba et al. 2003). Subjects underwent a neuropsychological examination comprising auditory verbal learning, trail making test A, symbol digit test, stroop test, grooved pegboard test, judgement of line orientation, Hooper Test of Visual Organization and the Controlled Oral Word Association Test. Furthermore HRQL

and mood questionnaires were completed by the subjects. Interestingly, only the patients with decompensated cirrhosis did worse than the controls in the neuropsychological tests. They showed an impairment of attention, executive function and motor performance. The test results of the patients with chronic hepatitis did not significantly differ from controls, even not in the verbal learning test, which had presented pathological results in HCV-infected patients in several other studies.

The second study with negative results with regard to cognitive dysfunction in HCV-infected patients included 103 HCV-PCR-positive hemophiliacs in the age of 6–19 years (Soogoor et al. 2006). The battery applied for neuropsychological testing included the Vineland Adaptive Behaviour Scales and the Wechsler Intelligence Scales. The Wechsler Digit Span was used as measure of attention/concentration.

Both studies included special sub-groups of patients. In J. Cordoba's study the diagnosis of HCV-infection had been made by chance in most of the subjects, when they had volunteered for blood donation. The study of Soogoor et al. (2006) on the other hand included children and young adults, exclusively. Thus, missing of neuropsychiatric alterations could be due to the short interval between infection and neuropsychological assessment.

Today there are only sparse data upon cognitive function in hepatitis B patients, and a frequently expressed criticism on the hypothesis of HCV-affection of the brain is the missing knowledge about cerebral function in hepatitis B patients. Karaivazoglou et al. (2007) assessed 32 Greek patients with hepatitis C with standardized neuropsychological measures and compared them to 20 healthy controls and 29 HBV-infected patients. The HCV-infected patients did significantly worse than the controls in the verbal memory and learning task, but they did not differ from HBV-infected patients. Psychomotor speed, attention and verbal fluency were unimpaired in both patient groups. The lack of significant differences between HCV- and HBV- infected patients in this study poses the question if cognitive dysfunction in HCV-infected patients is due to a direct effect of the virus or is an unspecific consequence of chronic viral hepatitis, that indicates that chronic viral liver disease even in the absence of cirrhosis may be associated with subtle cognitive decline.

An unspecific effect of chronic inflammation associated with chronic viral hepatitis, however, can not explain why chronic fatigue and cognitive dysfunction persist in several patients even after a successful clearance of the virus.

We compared HRQL scores, fatigue and depression scores and cognitive function in PCR-positive (n=47) and PCR-negative (n=22) HCV-infected patients and controls (n=26), and found similar cognitive deficits in both patient groups. In addition, both patient groups differed significantly from controls with regard to the SF36 scores, the fatigue and the depression scores, while again there was no significant difference between PCR-positive and PCR-negative patients.

In summary, several groups have shown cognitive deficits in HCV-infected patients with only mild liver disease. Cognitive impairment in these patients relates to attention and concentration ability and especially verbal learning ability, and is unrelated to the extent of fatigue, depression or the reduction of health related quality of life. As for fatigue the cause of cognitive dysfunction in HCV-infection is unknown. The fact that patients with chronic hepatitis B in the Karavaizoglou study

also presented with impairment of learning ability could be an indication for an unspecific effect of chronic liver inflammation on brain function. This hypothesis, however, does not explain why even part of the patients who have cleared the virus in the periphery and who have no ongoing liver disease suffer from persistent neuropsychiatric symptoms.

Neuroimaging in HCV-infected patients with neuropsychiatric symptoms

Up to now only a few neuro-imaging studies have been performed in HCV-afflicted patients.

Magnetic resonance imaging and spectroscopy (MRI/MRS)

Conventional magnetic resonance imaging of the brain was normal even in patients with severe fatigue and cognitive dysfunction (Forton et al. 2001, Weissenborn et al. 2004). Magnetic resonance spectroscopy, however, revealed changes in the cerebral metabolite spectrum in the basal ganglia, the white matter and the frontal cortex.

Forton et al. (2001) looked at cerebral choline/creatine (Cho/Cr) ratios in the basal ganglia, the white matter and the occipital cortex in 30 HCV-infected patients, 29 age-matched controls and 12 patients with chronic hepatitis B. They found significantly higher Cho/Cr ratios in the white matter and the basal ganglia of the HCV group compared to the hepatitis B group and the healthy volunteers. However, they could not show any associations between the MRS alterations and the grade of liver disease, liver enzyme levels, viral genotype or a history of intravenous drug abuse. Considering the fact that similar abnormalities have been documented in cerebral HIV infection, where the alterations are thought to be induced by microglia activation, Forton et al suggested that either HCV might infect the brain or the microglia activation was induced via peripherally derived cytokines. The spectra of the hepatitis B patients did not differ from controls arguing for pathophysiological differences between hepatitis B and hepatitis C with regard to brain function.

We looked for MRS alterations in 29 PCR-positive patients compared to 14 healthy controls (Weissenborn et al. 2004). Regions of interest were the basal ganglia, parietal white matter, frontal grey matter and pons. We found a significant decrease of the N-acetyl-aspartate/creatine (NAA/Cr) ratio in the frontal grey matter of the patients but no changes of the Cho/Cr ratio. Half of the patients suffered severe chronic fatigue. MRS changes and psychometric data, however, were not closely correlated.

While McAndrews et al. (2005) observed only slight deficits of the learning ability in their hepatitis C patients they nevertheless found significant cerebral MRS alterations in the same patient group. Spectra were achieved for the basal ganglia, the white matter and the frontal grey matter. In contrast to the two former studies they used the LCmodel (Provencher 1995) for spectra analysis. Thus, the comparability of the results between the different MRS studies is limited. But, interestingly McAndrews et al. found an increase in the choline content and a decrease in the NAA content in the white matter in the patients compared to controls. They found no

significant correlation between MRS alterations and liver disease severity markers or psychometric data.

Finally, the McAndrews data confirm the findings of both former studies, on principle, using a different method for data analysis. The data hint to an increased cell membrane turnover and decreased neuronal function.

Single photon emission tomography (SPECT)

Stimulated by the observation of E.A. Jones that chronic fatigue in hepatitis C patients disappears with ondansetrone therapy we started to look for alterations of serotonergic neurotransmission in hepatitis C patients, who were referred to our clinic because of disabling chronic fatigue and increasing cognitive dysfunction. We used I-123-Beta-CIT (2ß-carbomethoxy-3-ß-(4-[^{123}I]iodophenyl) tropane-single photon emission tomography (SPECT). Beta-CIT-SPECT provides the chance to study the mesencephalic/hypothalamic serotonin (SERT) and striatal dopamine transporter (DAT) binding capacity in vivo. When we observed alterations of both, serotonin and dopamine transporter binding, in part of the patients (Weissenborn et al. 2006) we included Beta-CIT-SPECT in further studies in hepatitis C patients. Meanwhile we hold data of 35 HCV-afflicted patients and 20 controls. The patients differ significantly from controls with regard to both, serotonin ($p<0.0001$) and dopamine ($p<0.0009$) transporter binding (Fig. 1). Fifteen patients achieved SPECT results within the normal range, 3 had a significantly decreased SERT binding, 10 a significantly decreased DAT binding and 7 a significantly decreased SERT *and* DAT binding.

Nine of the 35 patients were PCR-negative at the time of the examination. All patients had only slight if any liver disease. The distribution of normal and

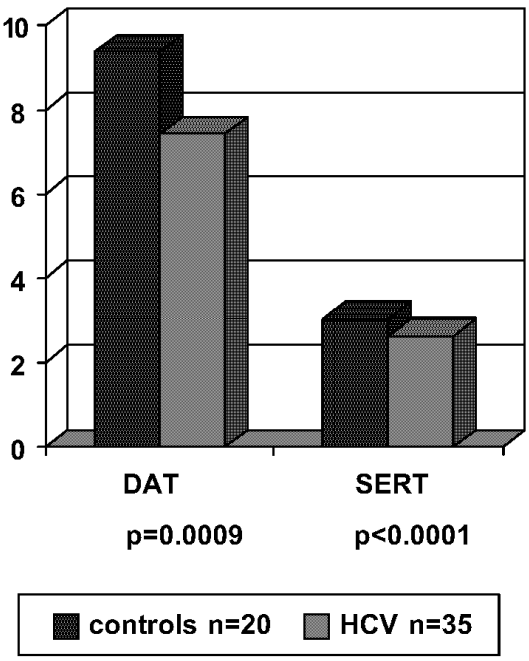

Fig. 1 DAT and SERT binding in 35 HCV-afflicted patients with no or only mild liver disease compared to healthy controls

pathological SPECT results was similar in PCR-positive and PCR-negative patients (PCR+: 42% normal SPECT; PCR-: 44.4% normal SPECT). Three of five PCR-negative patients with abnormal SPECT result had a pathological SERT and DAT binding, two only an abnormal DAT binding. Eight out of 14 PCR+ patients had a pathological DAT binding, three a pathological SERT binding and four, both, a pathological DAT and SERT binding. Interestingly, pathological SPECT results were associated with pathological psychometric results. While the patients with normal SPECT had also normal results in most of the attention tests, the patients with pathological DAT or DAT and SERT binding differed from controls especially with regard to the number of errors or missings in the attention tests (Fig. 2a,b). In contrast, all patient groups, irrespective of their DAT and SERT binding had significantly higher fatigue and depression scores than healthy controls (Fig. 3a,b).

Positron emission tomography (PET)

To our knowledge, two PET studies using 18F-fluoro-desoxy-glucose (FDG) as tracer have been performed in HCV-afflicted patients, so far. The aim of the first of those studies was the detection of changes in cerebral glucose metabolism during interferon therapy (Jüngling et al. 2000). Eleven patients with chronic active viral hepatitis underwent FDG-PET twice, directly before and after 3 months of Interferon-α-therapy. In addition to the PET examination the patients were asked to do the auditory verbal learning test, a verbal fluency test and the trail making test part A. In addition they had to fill in the HADS, BDI and SCL-90-R (Symptom Check List). PET data were analysed using SPM (statistical parametric mapping). PET before IFN therapy showed no divergence of the patients' cerebral glucose metabolism compared to the normal database. In the pair-wise comparison of the before and during therapy investigations, however, a significant hypometabolism became evident bilaterally in the prefrontal area and in the right parietal cortex. A hypermetabolism was detected in both putamina, the right thalamus and the left occipital area. The PET alterations were associated with an increase in the depression scores and a decrease in the results of the auditory verbal learning test. The hypometabolism in the prefrontal areas correlated with the BDI scores ($p<0.001$).

Unfortunately the psychometric test results of the patients were not compared to healthy controls in this study. The published data suggest that the patients were not disabled before the therapy started, neither with regard to cognition nor to mood disturbances. This assumption becomes relevant considering the data of the second FDG-PET study in HCV-afflicted patients, which has been performed by our group recently, and has not yet been published. The results of our study can be summarized as follows: Fifteen patients with a history of HCV-infection but no significant liver disease who complained of chronic fatigue and cognitive decline were studied. The patients showed significant attention and memory deficits compared to healthy controls. FDG-PET showed a decreased glucose metabolism in the patients compared to healthy controls especially in the limbic association cortex. A sub-division of the patient group into PCR-positive ($n=10$) and PCR-negative ($n=5$) patients and a comparison of the respective psychometric and PET data revealed no difference between the two patient groups, while both patient groups differed significantly from controls.

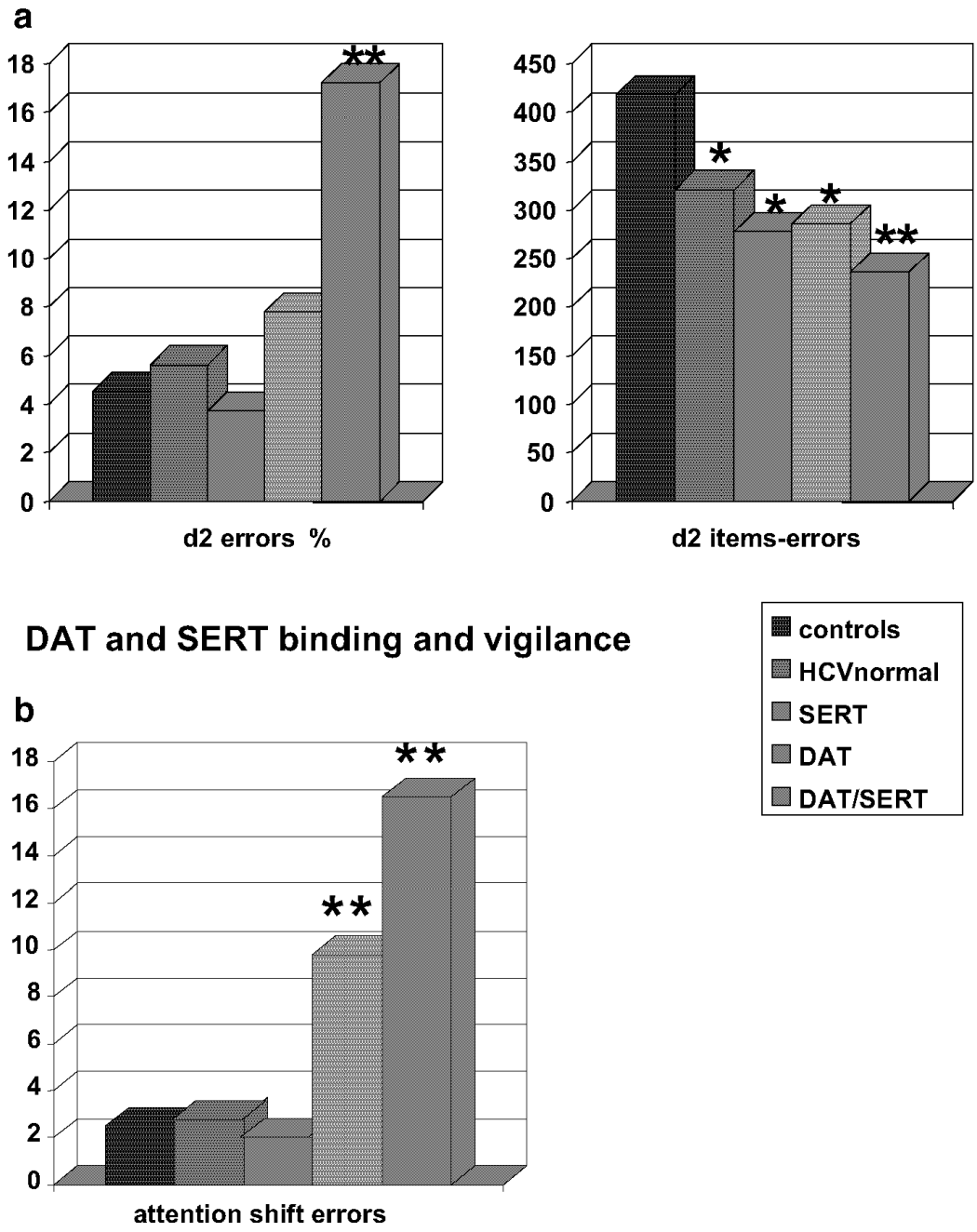

Fig. 2 Comparison of the cancelling d test results **a** and the number of errors in the attention shift test **b** between controls, patients with normal SPECT results, patients with pathological SERT binding, patients with pathological DAT binding, and patients with pathological DAT and SERT binding

In 2007 Grover et al. presented preliminary data of a [^{11}C] (R)-PK11195-PET study in 11 patients with biopsy-proven mild hepatitis C (International Symposium on Hyperammonemia and Hepatic Encehalopathy, Valencia, Spain, abstract). They hypothesised that patients with mild hepatitis C have increased microglia activation in the brain. In fact, they found a significant increase in the binding potential of [^{11}C] (R)-PK11195 in the caudate nucleus of the patients compared to healthy controls, and thus further evidence for an affection of the brain in HCV-infection.

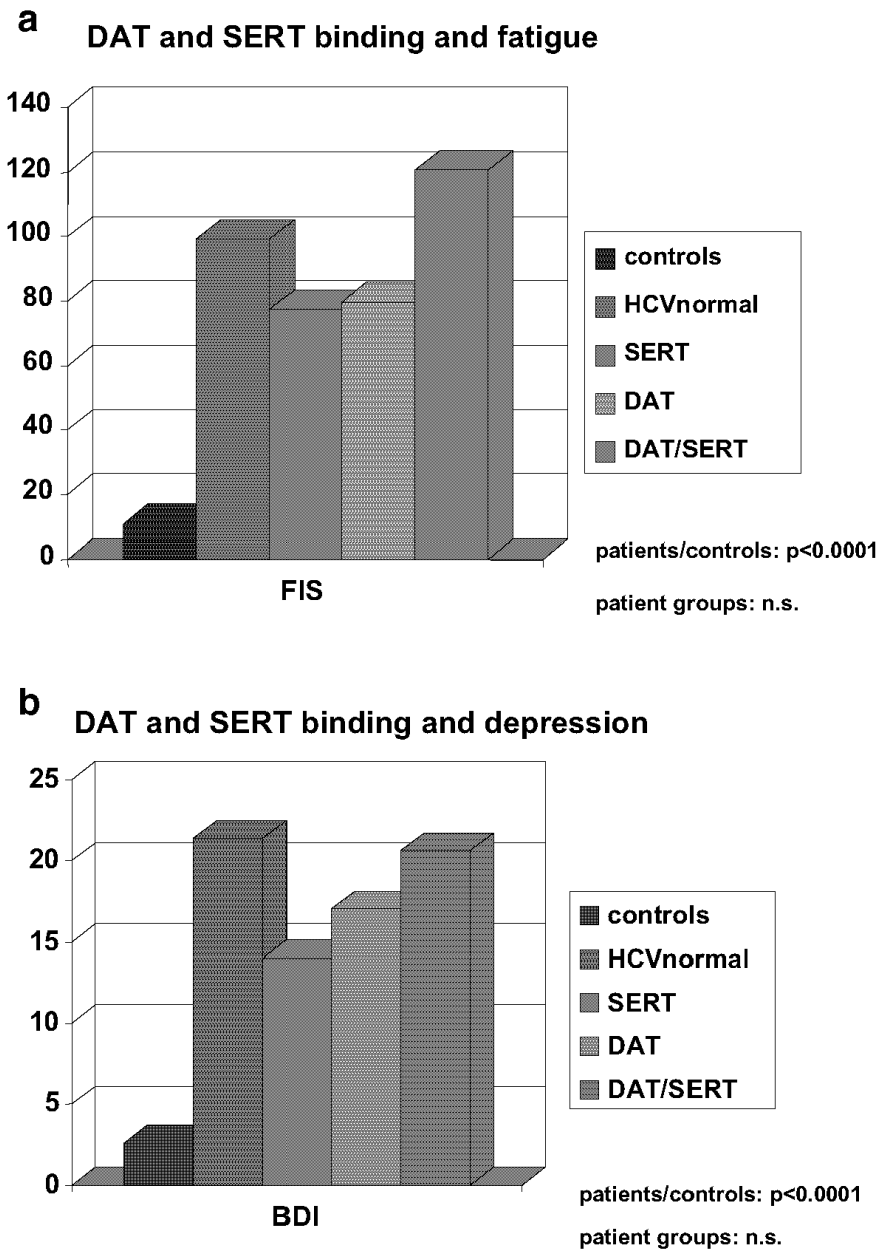

Fig. 3 Comparison of the fatigue score FIS (**a**) and the BDI score (**b**) between the different patient groups and controls

Cerebrospinal fluid (CSF)/brain biopsy

Up to now it is still unclear if the neuropsychiatric symptoms present in HCV-exposed patients relate to a direct HCV infection of the brain or to the unspecific reaction of brain cells to mediators of inflammation, such as cytokines (Forton 2006). Laskus et al. 2005 detected negative strand HCV-RNA, a viral replication intermediary, in autopsy brain tissue of three out of six HCV-infected patients. In two of these patients viral sequences amplified from the brain differed from those circulating in serum, thus indicating viral brain compartmentalization (Radkowski

et al. 2002; Laskus et al. 2005). Based on a sequence analysis of two different viral regions it was suggested that the brain-derived HCV variants were more closely related to the virus present in the lymphoid system than to virus present in serum. A close relationship between HCV variants present in brain tissue and in lymph nodes was also described by Forton et al. (2004). Adair et al. (2004) identified the brain cells harbouring HCV as macrophages/microglia. They separated brain cell types from autopsy brain tissue from two HCV-positive patients by laser capture microscopy, and found HCV-RNA positive and negative strands only in CD68-positive cells (macrophages/microglia).

It is suggested that HCV-infected macrophages/monocytes enter the brain via the blood-brain-barrier. Recent findings of HCV-infected cells in the cerebro-spinal fluid support this hypothesis. Laskus et al. (2002) found HCV-RNA in the cellular fraction of the CSF of eight out of 13 patients, but only in two out of 13 supernatants. Again the sequences of the brain (CSF) derived virus were closer to those found in peripheral blood mononuclear cells (PBMC) than to those circulating in serum in half of the patients.

Fishman et al. (2008) identified HCV in brain specimens of seven of 13 patients with viremia via 5′UTR (un-translated region) and E1 (envelope 1) gene analysis. They observed that several viral mutations present in clones from more than one brain region was absent in clones from liver and plasma. Interestingly the positive brain specimens had been sampled within 6.6 h (on average) after death, while the negative samples had been collected after 12.75 h on average. Thus, HCV RNA content in brain samples may continuously decrease after death.

Conclusion

A reduction of health related quality of life, chronic fatigue, depression and cognitive decline are characteristic complaints of HCV-infected patients even in the absence of significant liver disease. While the HRQL reduction and depression may be discussed as caused by a multitude of factors, both, biological and psychological, there is ample evidence that brain dysfunction is the main cause of fatigue and cognitive decline in the patients. It is suggested that alterations in brain function also play a major role with regard to mood alterations in the patients and with regard to HRQL. Today, the pathophysiology of the HCV-encephalopathy is still unclear. The detection of "brain-specific" virus sequences and the persistence of symptoms after clearance of the virus in the periphery, however, suggest direct HCV infection of the brain.

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