LACK OF ASSOCIATION BETWEEN HIPPOCAMPAL VOLUME REDUCTION AND FIRST-ONSET ALCOHOL WITHDRAWAL SEIZURE. A VOLUMETRIC MRI STUDY

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(Received 19 February 2002; first review notified 8 April 2002; in revised form 7 June 2002; accepted 8 July 2002)

Abstract — Aims and Methods: Magnetic resonance imaging (MRI) of the hippocampus has been extensively studied in both neurological and psychiatric disorders. Furthermore, hippocampal volume reductions on MRI have been reported in patients with chronic alcoholism. The present volumetric MRI study was undertaken to determine whether an association exists between hippocampal volume reduction and first-onset alcohol withdrawal seizure. Until recently, no data as to whether hippocampal volume reductions in alcoholics might serve as a predictor of withdrawal seizures were available. Results: We found the average hippocampal volumes measured by high resolution MRI to be significantly reduced in 52 alcoholics compared with 30 healthy controls. Besides a decrease of hippocampal volume in patients with chronic alcoholism, we could not find any significant correlation between the occurrence of seizures during alcohol withdrawal and the amount of hippocampal volume reduction in these patients. Conclusions: Thus, the alcoholism-related atrophy within the hippocampal formation in patients suffering from chronic alcoholism does not seem to be the source of convulsive activity in these patients. Neither does the amount of atrophy allow the occurrence of first-onset withdrawal seizures to be predicted.

INTRODUCTION

Magnetic resonance imaging (MRI) of the hippocampus has been extensively studied in both neurological and psychiatric disorders (Steffens and Krishnan, 1998). Hippocampal volume reductions on MRI have been reported in patients with chronic alcoholism (Sullivan et al., 1995; Agartz et al., 1999; Laakso et al., 2000). The alcohol withdrawal syndrome is a state of hyperexcitability characterized by a variety of neuropsychiatric disturbances such as anxiety, fear, muscular rigidity and generalized tonic-clonic seizures with epileptiform-type characteristics. Although the relationship between alcohol and epilepsy has been the focus of many reports (Chan, 1985; Hauser et al., 1988; Grant et al., 1990; Worner, 1996), many questions remain unanswered and the existence and pathogenesis of ‘alcohol epilepsy’ is still controversial. The classic view is that alcoholic seizures do not constitute a specific syndrome, since they occur mainly during withdrawal in chronic alcoholics (Victor and Brausch, 1967). Reflecting this conception, the International League Against Epilepsy (ILAE, 1989) classes the latter with other withdrawal seizures under the heading of ‘special syndromes’. Unfortunately, little is known about how to predict the course of alcohol withdrawal and alcohol withdrawal seizures. Until recently, various risk factors and/or predictors, such as repeated alcohol withdrawals (kindling model) (Brown et al., 1988), alcohol level on admission (Vinson and Menezes, 1991), hazardous alcohol drinking (Brathen et al., 1999), elevated homocysteine levels (Bleich et al., 2000a), genetic factors (Schaumann et al., 1994), age, duration of disease or previous cerebral damage (to list a few) have been discussed. However, most of the known predictors have proven to be of scarce utility.

Atrophy and/or morphological changes of the brain and certain brain areas are known to be excitatory focuses causing seizure activity. Chronic alcohol consumption can induce alterations in the function and morphology of most, if not all, brain systems and structures up to brain atrophy (Fadda and Rosetti, 1998; Kril and Halliday, 1998). Reduced white matter volume in the temporal lobe has been implicated as either causative or a result of seizures during alcohol withdrawal (Sullivan et al., 1996).

We used in the present study a high-resolution volumetric MRI technique to assess the decrease of hippocampal volume in patients with chronic alcoholism. The aim was to evaluate whether a reduction of hippocampal volume in these patients is associated with a higher incidence of seizures during the withdrawal state.

SUBJECTS AND METHODS

The present open and controlled study included 52 chronic alcoholics (aged 29–67 years; 34 males, 18 females) and 30 healthy subjects (aged 26–64 years; 16 males, 14 females). The study was approved by the local Ethical Committee. Clinical diagnosis and laboratory investigations were performed as described recently (Bleich et al., 2000a,b). In brief, all patients were active drinkers, had an established diagnosis of alcohol dependence according to the DSM-IV criteria (American Psychiatric Association, 1994), with a history of alcohol consumption ranging between 7 and 30 years (mean 13.1 years). All patients were detoxified in the detoxification unit, had stopped drinking right before admission, and were taking no drugs before being enrolled in the study. Patients were detoxified in all cases with the same psychotropis medication (clomethiazole). Patients who demonstrated signs of dementia (i.e. Korsakoff disease) or patients with any other substance misuse (positive urinary drug screen) were excluded. Patients with a history of repeated...
withdrawal episodes (>3) and/or previous withdrawal seizures were also not enrolled in the study, in order to avoid the confounding effects of repeated withdrawals on brain volume. The control group had no disorder meeting DSM-IV criteria. All patients and healthy subjects were right-handed. The patients with alcohol dependency underwent MRI within 10 days after admission.

**Brain MRI**

All MRIs were performed using a superconducting magnet at a field strength of 1.5 T (1.5 Tesla Gyroscan ACS NT; Philips, Germany). The T1-weighted coronal images (FFE-sequence) were acquired by means of a 256 × 256 matrix with a repetition time of 24 ms and an echo time of 6 ms. Data were visualized using Volume-Presentation-Software on the EasyVision Work Station (Philips).

Hippocampal volumes were measured according to the method used in the studies of Agartz et al. (1999) to render the imaging studies highly comparable. Therefore, the coronal sections of the hippocampus were reformatted to a series of 1.3-mm-thick sagittal sections by means of a cubic spline interpolation. The reformatted sagittal sections were contiguous. The three-dimensional reconstruction was obtained by isosurface rendering. The hippocampus was outlined manually in the sagittal sections. The number of sections used to complete a hemisphere was 17 (14–19) on the right as well as on the left side. Measurement reliability: two operators independently measured the hippocampus in all cases, whereby these measurements were done blind to the study groups. The intra-class correlation was determined for the right ($r = 0.92$ and $r = 0.90$, respectively) and the left ($r = 0.89$ and $r = 0.94$, respectively) hippocampal volumes.

**Statistical analysis**

Comparisons between patients with alcoholism and healthy controls were made using the $t$-test for independent samples (two-tailed). The results are presented as the means ± SD. Analysis of variance (ANOVA) was performed to assess the effects of dichotomous variables (withdrawal seizure, gender) and covariates (age, body mass index, lifetime drinking, years of drinking) on the patients’ hippocampal volumes. A $P$-value of less than 0.05 was considered significant.

**RESULTS**

As illustrated in Fig. 1a, b and shown in Table 1, average hippocampal volumes (HCtotal) (mean of sum of the left and right hippocampal volume), right (HCright), and left (HCleft) hippocampal volumes were found to be significantly reduced in alcoholics, compared with the control group ($t = -7.351$ to $-7.769$; $df = 80$; $P < 0.0005$). The mean value (± SD) within the patients’ group ($n = 52$) was $3.064 ± 0.487$ ml (range $2.077–4.129$ ml) compared to $3.856 ± 0.358$ ml (range $3.165–4.621$ ml) with the control group ($n = 30$). Other factors which can influence brain volume, such as body mass index ($t = 1.075$; $P = 0.286$) or age ($t = -0.674$; $P = 0.503$) revealed no differences among the groups.

In total, 16 of the 52 alcoholics (31%) suffered from a first-onset withdrawal seizure; three of 18 women (16%) and 13 of 34 men (38%). To avoid confusion between brain size and gender, male and female patients were analysed separately.

![Figure 1a](image1a.png) ![Figure 1b](image1b.png)

**Figure 1a**

**Figure 1b**

Fig. 1. Comparison of hippocampal volumes.
The MR images demonstrate the outlined hippocampal area contours in the sagittal plane. The size of hippocampal and brain structures in controls (a) was significantly larger than the hippocampal size of patients with chronic alcoholism (b). Statistical details are summarized in Table 1.
For descriptive and statistical results within the group of alcoholics see Tables 2 and 3. We ran ANOVAs to analyse the effect of first-onset seizures during alcohol withdrawal on hippocampal volumes: we did not observe any significant findings in the alcoholic patients either for the right ($F = 0.37, P = 0.549$) or the left ($F = 1.80, P = 0.186$) hippocampus, nor for the average hippocampal volume ($F = 0.97, P = 0.331$). In addition, analysis of the influence of seizure by gender on hippocampal volumes revealed no significant results ($F = 0.81–1.69, P = 0.200–0.372$, see Table 3). As shown in Table 2, female patients had smaller hippocampal volumes than male patients, however, this was not linked to the occurrence of withdrawal seizures rather than to an expected and known sex difference. Therefore, statistical analysis (ANOVA) showed that gender itself had a trend for hippocampal volume reduction with respect to the right hippocampal volume ($F = 3.35, P = 0.074$) and for the average hippocampal volume ($F = 3.28, P = 0.077$). Analysis of covariates showed a significant correlation between body mass index and hippocampal volumes ($F = 4.28–5.42, P = 0.017–0.045$). We found a trend for the influence of years of drinking on hippocampal volume reduction in the left hippocampus ($F = 3.73, P = 0.060$) and for the average hippocampal volume ($F = 3.36, P = 0.077$). Spearman’s rho: males, $r = –0.313, P = 0.072$; females, $r = –0.373, P = 0.127$ (Table 3 and Fig. 2). No significant influence of age or lifetime alcohol consumption was observed.

**DISCUSSION**

As expected, we found a significant decrease of hippocampal volume in patients suffering from chronic alcoholism.
compared with healthy controls. These results are consistent with previous observations concerning hippocampal volume deficits in chronic alcoholics (Sullivan et al., 1995; Agartz et al., 1999). Recently, it has been observed that, in chronic alcoholism, the reduction of hippocampal volume is proportional to the reduction of brain volume (Agartz et al., 1999). Thus, the observed decrease in hippocampal volume might represent brain atrophy in chronic alcoholism rather than morphological changes in a certain brain area. However, the results of the present study revealed no significant association between volume loss in the hippocampal area and the occurrence of seizures during alcohol withdrawal in patients suffering from chronic alcoholism. The present findings validate previous studies concerning a lack of association between withdrawal seizures and hippocampal volume loss in patients with chronic alcoholism, even though a loss of white matter in the temporal lobe was found in patients with withdrawal seizures (Sullivan et al., 1996). Furthermore, this study is rather limited, taking into account the relatively small number of patients and the small number of female patients suffering from withdrawal seizures. In addition, only single measurements with an investigation of changes in a single brain area were taken at baseline, whereas repeated specimens and analysis of different brain structures may have given more precise results.

Withdrawal from chronic ethanol ingestion causes changes in hippocampal excitability (Morton et al., 1992) resulting in a state of hyperexcitability (Brailowsky and Garcia, 1999). Neuronal hyperexcitability following chronic ethanol exposure likely results from a variety of compensatory alterations in both excitatory and inhibitory signalling systems. Glutamate is the neurotransmitter at the majority of excitatory synapses in the mammalian CNS (Dodd et al., 2000). One of the more prominent systems sensitive to ethanol exposure involves glutamatergic excitatory synaptic neurotransmission mediated through the activation of a specific glutamate receptor subtype, the N-methyl-D-aspartate (NMDA) receptor (Thomas and Morissett, 2000). It has been shown that chronic ethanol treatment leads to an up-regulation of NMDA receptors, resulting in triggered rebound activation of receptor-mediated neurotransmission during the withdrawal state (Kril and Halliday, 1998). Therefore, the present results are consistent with the hypothesis that the up-regulation of NMDA receptor systems following chronic alcohol consumption may mediate the seizures associated with ethanol withdrawal, rather than morphological changes such as hippocampal atrophy. Fitting into this model would be the previous observation that, in alcoholics, the volume reduction occurs only in the white matter and that no neuronal loss occurs following chronic ethanol ingestion (Harding et al., 1997).

In conclusion, the results of the present study confirm that the hippocampal formation is vulnerable to alcohol-induced pathological changes. However, this alcoholism-associated atrophy within the hippocampal formation in chronic alcoholic patients does not seem to be the source of the convulsive activity in these patients. Neither does the extent of atrophy allow the occurrence of first-onset withdrawal seizures to be predicted. However, further extending investigations on different brain areas are needed to clarify the role of morphological changes and brain damage in chronic alcoholics in seizure development.

REFERENCES


