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Enlarged Cerebrospinal Fluid Spaces in Opiate-Dependent Male Patients: A Stereological CT Study

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Key Words
Computed tomography
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Abstract
Computed tomography was performed in 9 male patients with a diagnosis of opiate dependence and in 9 age-matched psychiatric controls (neurotic depression). Patients with a history or diagnosis of another substance dependence (alcohol, cocaine, cannabis) were excluded from the study. The volumes of internal and external components of cerebrospinal fluid (CSF) were measured with a point-counting stereological method. Analysis of variance with age as a covariate revealed a significant enlargement of external and external CSF spaces in male patients with opiate dependence. There was no significant correlation between the length of opiate dependence and the volumes of internal and external CSF spaces. The present results suggest that opiate dependence is associated with structural brain alterations. However, the relationship between opiate dependence and structural brain changes is complex and still not well understood.

Introduction

The effects of the chronic use of opioids on brain structures have not yet been extensively studied. Strang and Gurling [1] have found evidence of cerebral atrophy in a qualitative computed tomography (CT) study. Using functional brain imaging, several abnormalities of cerebral blood flow have been reported [2–4].

However, other studies [5, 6] found no evidence of ventricular enlargement or cortical atrophy in patients with opioid dependence. However, all these studies have used linear measurements (Evans ratio, ventricle:brain ratio) in order to estimate the ventricle size while for the examination of cortical atrophy they used only qualitative methods. Linear methods were found to be poorly correlated with ventricular volume [7].

The aim of the present study was to find out by means of volumetric determination of subarachnoid and ventricles spaces whether patients with opioid dependence had enlarged external and internal cerebrospinal fluid (CSF). For this purpose we used a point-counting stereological method [7]. This method has been validated in postmortem and phantom studies [8, 9]. Another purpose of the present study was the analysis of the relationship between alterations of brain structures and the length of opiate dependence.

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Table 1. Values of subtotal volumes of the external and internal CSF spaces in opioid-dependent patients (n = 9) and controls (n = 9)

	Opiate-dependent patients	Controls	Differences (%)	Analysis (d.f. = 2)	
				F	p
External CSF spaces	78.9 ± 42.7	55.4 ± 17.8	+42.3	3.82	0.045
Internal CSF spaces	81.8 ± 36.5	61.6 ± 23.5	+32.7	3.73	0.048

Volumes are given as means ± SD in cm^3. Differences (%) are expressed in relation to the controls.

Differences between the two groups were examined by using ANOVA with age as covariate.

Methods

Subjects

Nine male patient with an ICD-9 diagnosis of heroin dependence (mean age = 28.1 years) and 9 male psychiatric controls (mean age = 28.2 years) with an ICD-9 diagnosis of neurotic depression were included in the present study. All patients were admitted to the Psychiatric Department of the University of Bonn between September 1991 and December 1992. Subjects with a diagnosis of neurotic depression were included in the study as a control group since it has been shown that these persons show no enlargement of CSF spaces [10]. There were no significant differences (p = 0.98; Student's t test) in age between the two comparison groups.

Exclusion criteria for opiate-dependent subjects and control subjects were neurological signs or a history of neurological disease, head trauma, cardiovascular or endocrinological disease, current medical illness, seropositive status for the human immunodeficiency virus. The opiate-dependent subjects' exclusion criteria were established by an ICD-9 diagnosis of dependence on or abuse of any substance other than heroin, nicotine or caffeine. Urine toxicology testing was used on test days. These criteria were used to control potential confounding effects of other substances.

The mean duration of heroin dependence was 5.7 years (SD = 3.7). The average amount of daily street heroin was 1.1 g/day (SD = 0.4).

Ethics

The study was approved by the Ethical Committee of the University of Bonn. All patients gave their written informed consent to participate in this study.

CT Image Technique

Patients underwent an unenhanced cranial CT on a Siemens Somatom DRH scanner (Siemens, Erlangen, Germany) with axial cuts of 8-mm slice thickness, parallel to the orbitomeatal line. No tumors, infarctions, hematomas were found on the CT scan.

We considered subtotal but defined volumes of the external and internal (third + lateral ventricles) CSF spaces. Seven consecutive axial CT cuts were used. The level of the first scan was at the base of the skull through the cisterna interpeduncularis. For the assessment of the volumes a stereological method based on the Cavalieri [11] theorem of systematic sampling and adapted by Pakkenberg et al. [7] was used.

The volumes were calculated as follows: A transparent counting-grid was randomly placed on the CT scan and all points (p) hitting the external and internal CSF spaces were systematically counted. If the point-spacing of the grid is i mm, each grid point represented an area of $i \times i\ mm^2$, which was corrected for by the linear magnification (m), known from the CT scale. The sum of all points in all CT slices (Σp) gave a statistically representative estimate of the total area of the CSF spaces which, multiplied by the thickness of the slices (t), was easily converted into an estimate of the real volume (V). The formula

$$V = (\Sigma p + pmax) \times (i \times m)^2 \times t_n,$$

in which p_{max} is the maximal number of grid points counted on one slice, limits the bias of underprojection of a region of interest through a thick scan plane [7]. For the assessment of the CSF spaces we chose a grid size of $1 \times 1\ mm^2$. The investigator (T.B.) was blind to the diagnosis. To establish interrater reliability, nine randomly chosen CTs of brains were remeasured some months later by another author (P.D.). This investigator was also blind to the diagnosis. Intraclass correlations [12] with external and internal CSF regions ranged from 0.82 to 0.91.

The present method was validated in a previous study [13] with precision better than 2.5% for volumes ranging from 55 to 300 cm^2.

Statistical Analysis

Pearson product-moment correlations were performed between age and the calculated volumes of external and internal CSF spaces in all subjects (heroin-dependent subjects and controls) to assess the effect of age as potential confounding variable. In the opiate-dependent subjects Pearson correlations were also performed between length of illness and the calculated volumes of the external and internal CSF spaces.

Analysis of variance was performed to compare the volumes of CSF spaces and those between both groups. The significance level was set at $p < 0.05$. Calculations were made using the SPSS/PC+ 4.01 statistical package (SPSS Inc., Chicago, Ill., USA).

Results

The stereological analysis revealed that patients with opiate dependence had larger external (+42.3%) and internal CSF spaces (+32.7%) (table 1). We found significant positive correlations between age and external CSF spaces (r = 0.45; p = 0.05) and internal CSF spaces (r =

0.46; p = 0.04) in all subjects (n = 18). Therefore, analysis of variance (ANOVA) with age as covariate was performed to compare the volumes of CSF spaces between both groups. ANOVA revealed significantly enlarged external CSF spaces (F = 3.82, d.f. = 2, p = 0.04) and internal CSF spaces (F = 3.73, d.f. = 2, p = 0.04) in the heroin-dependent patients.

The length of illness was significantly correlated (r = 0.80, p = 0.009) with the age of the opiate-dependent patients. No significant correlations were found between the length of opiate dependence and external CSF spaces (r = 0.49, p = 0.17) or internal CSF spaces (r = 0.46, p = 0.20) in the opiate-dependent patients.

Discussion

The major finding in this study is an enlargement of external and internal CSF spaces in male patients with opioid dependence. The present study has certain advantages over previous work. In all of the previous studies opiate-dependent subjects were also dependent on other drugs such as cocaine, tranquilizers, barbiturates, etc. This is a potentially significant confounding variable, since it has been shown that drugs such as cocaine [14] or amphetamine [15] are related to structural cerebral atrophy. Another limitation of these studies is the use of qualitative methods and of linear measurements, since it is known that linear measurements are poorly correlated with ventricular volume [7].

The results of these studies of brain morphology in patients with opioid dependence were inconclusive: Strang and Gurling [1] found a widening of the Sylvan and interhemispheric fissures in a small sample of heroin addicts. In the CT study by Cascella et al. [6], the use of heroin showed no significant influence on the ventricle: brain ratio or sulcal width. No enlargement of the CSF spaces was reported in the study of Hill and Mikhael [5].

The following methodological limitations could have influenced the present results. One bias of the present study is the use of patients with a neurotic depression as a control group in comparison with the opiate-dependent male patients, since some, although not all, of the studies [16] have found enlargement of CSF spaces in depressive disorders [17]. However, in a recent planimetric CT study, Baumann et al. [10] found no enlargements of external or internal CSF spaces in male neurotic-depressive patients. However, these possibly enlarged CSF spaces in the control group would rather support our findings, since they imply that opiate-dependent patients have enlarged CSF spaces even in comparison with a group of subjects with rather large CSF spaces.

Another limitation of the present study is the small sample of subjects in the study. Since the majority of opiate-dependent subjects polydrug abusers [18], it is difficult to recruit subjects which are only opiate-dependent.

Another limitation of the study is the fact that length of illness was assessed in a retrospective manner only. However, the correlation between age and length of illness was highly significant, which makes this data more plausible.

The mechanisms underlying sulcal and ventricular enlargement cannot be ascertained but are probably diverse including a direct effect of opioids on brain metabolism [19, 20]. Animal studies have shown evidence for a role of endogenous opioids and morphine in controlling neural growth by inhibiting the proliferation of dendrites and dendritic spines [19].

The hypothesis that several drugs including opiates have an impact on neuronal growth mechanisms is consistent with the findings on brain atrophy due to alcohol dependence: Mann et al. [21] suggested that these changes were related to neuronal plasticity mechanisms.

It is not likely that the changes found in the present study are due to dehydration, since Amass et al. [22] reported no changes of T1 and T2 relaxation times in heroin- and cocaine-dependent men.

Another mechanism of brain atrophy could be due to malnutrition and weight loss [23]. Multiple vascular accidents, which have been demonstrated to occur in cocaine abusers and could lead to cerebral atrophy [24], were not shown on the CTs of the present study. Other factors, such as recurrent trauma associated with chronic drug abuse may contribute to the pathological findings [14].

In conclusion, the present results of enlarged CSF spaces in opiate-dependent male patients are partly consistent with previous CT studies in opiate addicts. However, the pathophysiology of structural brain changes in opiate dependence is still poorly understood. The data of the present investigation suggest the need for further long-term brain imaging studies in patients with opioid dependence.

References

1 Strang J, Gurling H: Computerized tomography and neuropsychological assessment in long-term high-dose heroin addicts. Br J Addict 1989;84:1011–1019.

2 Krystal JH, Woods SW, Kosten TR, Rosen MI, Seibyl JP, van-Dyck CC, Price LH, Zubal IG, Hoffer PB, Charney DS: Opiate dependence and withdrawal: preliminary assessment using single photon computerized tomography (SPECT). Am J Drug Alcohol Abuse 1995;21: 47–63.

3 Rose JS, Branchey M, Buydens-Branchey L, Stapleton JM, Chasten K, Werrell A, Maayan ML: Cerebral perfusion in early and late opiate withdrawal: a technetium-99m-HMPAO SPECT study. Psychiatry Res 1996;67:39–47.

4 Danos P, Kasper S, Grünwald F, Klemm E, Krappel C, Broich K, Höflich G, Overbeck B, Biersack HJ, Möller HJ: Pathological regional cerebral blood flow in opiate-dependent patients during withdrawal: A HMPAO-SPECT study. Neuropsychobiology 1998;37:194–199.

5 Hill SY, Mikhael MA: Computerized transaxial tomographic and neuropsychological evaluations in chronic alcoholics and heroin abusers. Am J Psychiatry 1979;136:598–602.

6 Cascella NG, Pearlson G, Wong DF, Broussolle E, Nagoshi C, Margolin RA, London ED: Effects of substance abuse on ventricular and sulcal measures assessed by computerised tomography. Br J Psychiatry 1991;159:217–221.

7 Pakkenberg B, Boesen J, Albeck M, Gjerris F: Unbiased and efficient estimation of total ventricular volume of the brain obtained from CT-scans by a stereological method. Neuroradiology 1989;31:413–417.

8 Mayhew TM, Olsen DR: MRI and model free estimates of brain volume determined using the Cavalieri principle. J Anat 1991;178:133–144.

9 MacFall JR, Byrum CE, Parashos I, Early B, Charles HC, Chittila V, Boyko OB, Upchurch L, Krishnan KRR: Relative accuracy and reproducibility of regional MRI volumes for point-counting methods. Psychiatry Res 1994; 55:167–177.

10 Baumann B, Bornschlegl C, Krell D, Bogerts B: Changes in CSF spaces differ in endogenous and neurotic depression. A planimetric CT scan study. J Affect Disord 1997;45:179–188.

11 Cavalieri B: Geometria degli indivisibili. Torino, Unione Tipographico, 1966.

12 Fleiss JC: The design and analysis of clinical experiments. New York, Wiley, 1986.

13 Van Roost D, Solymosi L, Funke K: A characteristic ventricular shape in myelomeningocele-associated hydrocephalus? A CT stereology study. Neuroradiology 1995;37:412–417.

14 Pascual-Leone A, Dhuna A, Anderson DC: Cerebral atrophy in habitual cocaine abusers: A planimetric CT study. Neurology 1991;41:34–38.

15 Rumbaugh CL, Fang HCH, Wilson GH, Higgins RE, Mestek MF: Cerebral CT findings in drug abuse: Clinical and experimental observations. J Comput Assist Tomogr 1980;4:330–334.

16 Van den Bossche B, Maes M, Brussaard C, Schotte C, Cosyns P, De Moor J, De Schepper A: Computed tomography of the brain in unipolar depression. J Affect Disord 1991;21:67–74.

17 Elkis H, Friedmann L, Wise A, Meltzer HY: Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Arch Gen Psychiatry 1995;52:735–746.

18 Darke S, Hall W: Levels and correlates of polydrug use among heroin users and regular amphetamine users. Drug Alcohol Depend 1995; 39:231–235.

19 Hauser KF, McLaughlin PJ, Zagon IS: Endogenous opioid systems and the regulation of dendritic growth and spine formation. J Comp Neurol 1989;281:13–22.

20 Pérez-Navarro E, Alberch J, Arenas E, Marsal J: Nerve growth factor and its receptors are diffentially modified by chronic naltrexone treatment during rat brain development. Neurosci Lett 1993;149:47–50.

21 Mann K, Mundle G, Langle G, Petersen D: The reversibility of alcoholic brain damage is not due to rehydration: A CT study. Addiction 1993;88:649–653.

22 Amass L, Nardin R, Mendelson JH, Teoh SK, Woods BT: Quantitative magnetic resonance imaging in heroin- and cocaine-dependent men: A preliminary study. Psychiatry Res 1992;45:15–23.

23 Hoffmann GW, Ellinwood EH Jr, Rockwell WJK, Herfkens RJ, Nishita JK, Guthrie LF: Cerebral atrophy in bulimia. Biol Psychiatry 1989;25:894–902.

24 Klonoff DC, Andrews BT, Obana WG: Stroke associated with cocaine use. Arch Neurol 1989; 46:989–993.