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Cerebral atrophy in AIDS: a stereological study*

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Summary. Stereological estimates of mean volumes, surface areas, and cortical thicknesses were obtained on formalin-fixed brains from 19 men with AIDS and 19 controls. Volumes of neocortex, white matter, central brain nuclei, ventricles and archicortex were estimated using point counting and Cavalieri's unbiased principle for volume estimation. In AIDS, the mean volume of neocortex was reduced by 11 %, and that of the central brain nuclei by 18 %. Mean ventricular volume was increased by 55 %. Mean neocortical thickness was reduced by 12 %. The mean volume of white matter was reduced by 13 %. The findings in 6 clinically demented AIDS patients were not statistically different from the rest of the group.

Key words: Acquired immune deficiency syndrome (AIDS) – Cavalieri's principle – Cerebral atrophy – Morphometry – Stereology

Brain atrophy is a common but not constant finding in patients with acquired immune deficiency syndrome (AIDS) [1, 7, 8, 12, 19, 22, 23, 31]. Various structures are affected and to a varying degree. Both cortical atrophy – diffuse or located to one or more lobes – and central atrophy is commonly found on computerized axial tomography (CT), on magnetic resonance imaging (MRI), or at postmortem examination [4, 15, 18, 19, 20, 23, 27, 30, 32], sometimes combined with ventricular enlargement. A few authors have mentioned reduction of the white matter [21, 24, 30]. Atrophy may be the only cerebral abnormality [26] and seems to be a morphological feature in HIV_1-associated cognitive/motor complex [3] (AIDS dementia complex) [4, 22, 24, 27].

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Quantitation on autopsy brains has mainly been based on brain weight, which may be taken as an indication of pathological changes when related to the body height and weight, age and sex [5, 13, 14, 25]. The brain weight was low in cases that appeared atrophic at autopsy, but a significant reduction in the AIDS patients has not been shown [6, 12], although demented patients tend to have brain weight below normal [22].

Attempts to evaluate cerebral atrophy have been done using planimetry on MRI [4] and on CT scans [7]; using computerized image analyzer neocortical width has been reported to be decreased by 20 % in brains affected by human immuno-deficiency virus (HIV) encephalitis compared to HIV-seropositive controls [34]. However, unbiased stereological principles have not previously been used to estimate the volume of macroscopic parameters on brains from AIDS patients.

Application of Cavalieri's principle [10] and stereological methods introduced in the 1980s have made such measurements more precise with less effort. According to Cavalieri's principle [10], the volume of even arbitrarily complex structures can be estimated from the sum of parallel areas separated by a known distance, provided the set of sections is positioned at random on the chosen axis. Profile areas are most efficiently estimated by point counting [10, 11, 33]. The points must hit the structure in a systematically random way. Thus, volume estimates of various macroscopic regions in a human brain can be obtained with a coefficient of error (CE = SEM/mean) between 5 % and 15 % in less than 2 h [29].

Material

One complete cerebral hemisphere from each of 19 HIV-infected men were studied: 12 right and 7 left (left hemispheres were often damaged during evisceration). The patients had died from November 1986 to May 1989. The age range was 20–67 years (median 43 years). Of the patients studied 16 were homo- or bisexual, in 3 the route of infection was not known. Drug abusers, alcoholic addicts and patients with intracranial tumors (neoplastic and non-

neoplastic) were excluded, as were patients with preexisting diseases that may affect the brain, such as epilepsy and severe hypertension. The time from a positive serotest for HIV to death was 2–42 months (median 10 months). Of the patients 16 had opportunistic infections: 4 had Kaposi sarcoma, 3 had malignant lymphomas without brain involvement, 2 had neurological symptoms referable to the brain, and 6 were clinically demented. All had lost some body weight. Eight patients were described as emaciated, in 8 the nutritional status was within normal limits, in 3 it was not noted in the autopsy reports. Autopsies were performed 13–73 h post mortem (median 23 h). The primary cause of death was pneumonia in 16 cases [mostly caused by cytomegalovirus (CMV) and/or pneumocystis carini], and widespread Kaposi sarcoma involving the lungs in 3 cases. The control group was 19 age-matched men without known mental or neurological disease who died from non-cerebral vascular, cardiac or pulmonary diseases, or suffered a violent death. The median body height was 176 cm (177 to 192 cm) in the patients, and 180 cm (167 to 193 cm) in the controls. The brains were stored in buffered neutral 10 % formalin for at least 5 months. The fixed brains weighed 1110–1670 g (mean 1385 g) in the AIDS group, 1185–1580 g (mean 1442 g) in the controls.

Light microscopy showed microglial nodular encephalitis in nine cases (CMV demonstrated in five), cryptococcal meningoencephalitis in one case, meningoencephal aspergillosis in one case, HIV encephalitis (as defined in [3]) in two cases. This may be a minimum as only routine sections were taken, including two sections from centrum semiovale. Gliosis and edema was seen in all brains, and was the only abnormality in seven. Major findings in the HIV patients are listed in Table 1.

Methods

Brain stem and cerebellum was cut through mesencephalon. The cerebral hemispheres were divided through corpus callosum, and the hemisphere for morphometry was rinsed in running tap water overnight. Meninges were removed. To facilitate identification on the cut surfaces the pial surfaces of the parietal, temporal,

Table 1. Major findings in the HIV-positive patients

Age (years)	Hight (cm)	HIV+ (months)	Clinical findings	Autopsy major findings	Neuropathological findings incl. fixed brain weight
46	192	< 1	Hodgkins ML	Hodgkins ML, PCP	1100 g, edema, gliosis
20	170	30	Kaposi sarcoma, PCP	Kaposi sarcoma	1320 g, edema, gliosis
52	184	6	Immunoblastic ML	Immunoblastic ML, PCP, CMVP	1435 g, edema, gliosis
40	187	36	PCP, CMVP	PCP, CMVP	1470 g, edema, gliosis, microinfarction
43	175	6	Esophagitis (CMV, Candida), perianal herpes, emaciation, dementia	Pneumonia	1385 g, HIV encephalitis
46	176	5	Pleural effusion, intestinal Kaposi sarcoma	Kaposi sarcoma	1670 g, edema, gliosis
26	173	6	Pneumonia (atypical TB), polyneuropathy, emaciation	Pneumonia	1275 g, microglial nodular encephalitis
56	182	37	Large cell ML, emaciation, dementia	Large cell ML pneumonia	1450 g, edema
40	181	5	Chronic herpes, oral candidiasis, emaciation	PCP	1280 g, microglial nodular encephalitis
56	183	4	PCP, emaciation, dementia	CMVP	1370 g, CMV encephalitis, HIV encephalitis, edema
37	183	23	Kaposi sarcoma, PCP	Kaposi sarcoma, CMVP	1290 g, CMV encephalitis
40	169	10	PCP, diarrhoea, emaciation	CMVP, CMV colitis	1280 g, CMV encephalitis, gliosis
67	168	6	Candida oesophagitis, cryptococcosis, dementia	PCP	1340 g, edema, gliosis
66	170	< 1	Pneumonia, mediastinal emphysema, emaciation	Pneumonia	1350 g, microglial nodular encephalitis
32	185	26	PCP, emaciation, dementia	Pneumonia	1465 g, meningoencephalitis (Cryptococcus)
51	170	24	PCP, herpes zoster, CMV retinitis	CMVP	1455 g, microglial nodular encephalitis
41	175	12	Kaposi sarcoma, PCP, CMVP	Kaposi sarcoma, macronodular cirrhosis of the liver	1480 g, edema
48	181	16	PCP, tub.pulm.	Lung aspergilloma, PCP, widespread CMV	1465 g, CMV encephalitis, meningoencephal aspergillosis
57	170	42	PCP, syphilis, CMV cystitis, dementia	CMVP	1370 g, CMV encephalitis

PCP, Pneumocystis carini pneumonia; CMV, cytomegalovirus; CMVP, cytomegalovirus pneumonia; ML, malignant lymphoma; tub. pulm., tuberculosis of the lung

occipital, and archicortex[1] were painted with ink, each in a different color as illustrated in [2, 28] before embedding in 5% agar to keep loose fragments in place after cutting. Hemispheres were cut frontally in slices of an average of ~7 mm starting randomly at the frontal pole. The average thickness of the slices was estimated from the total fronto-occipital length of the hemisphere divided by the number of slices.

A transparent counting grid (Fig. 1) with points and test lines was placed at random over the occipital cut surface of every brain slice. The volumes were calculated from Cavalieri's principle:

$V = \bar{t} \times a(p) \times \Sigma P$

where V = total volume of the structure, $\bar{t}$ = the average slice thickness, a(p) = the area per point (i.e., the area in cm^2 corresponding to each point on the counting grid), and ΣP = the total number of points hitting the structure.

The surface areas were estimated from:

$$S = \frac{2 \times \Sigma I \times V(ref)}{\Sigma P \times l(p)}$$

where S = total surface of the structure, V(ref) = volume of cortex of the structure, ΣI = total number of intersections between a test line and the pial surface of cortex, ΣP = total number of points hitting the cortex of the structure, and l/p = test line length per point. The above equation assumes that the pial surface is isotropic.

The cortical thickness of the region is the volume of cortex divided by the surface area.

Statistics

Group means were compared using Student's *t*-test for unpaired observations. Variability within groups was indicated using both the standard deviation (SD) and the dimensionless coefficient of variation (CV = SD/mean). Ventricular volumes were analyzed after logarithmic transformation and results are given in terms of geometric means and CV. Ventricular volumes were positively correlated to age in both groups, but due to differing slopes in the two groups, the regression was ignored when comparing the geometric mean values. A $2P$ value of 0.05 was adopted throughout.

CE calculated from equation 6 in [10] was used to check the reliability of measurements during collection of data.

[1] Uncus, hippocampus, parahippocampal gyrus, gyrus fornicatus, subcallosal area. Amygdala was included in archicortex.

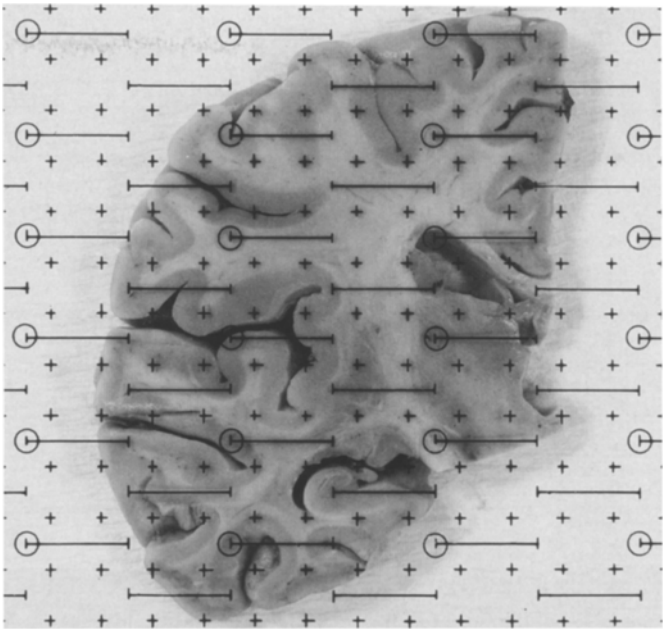

Fig. 1. A brain slice with transparent grid superposed. The grid has "fine" points with a distance of 0.75 cm, corresponding to an area of 0.5625 cm^2/point, and "coarse" points at both ends of test lines with a distance of 1.5 cm and 0.75 cm, corresponding to an area of 1.125 cm^2. To estimate volume, fine points were counted over small structures, i.e., occipital lobe, archicortex, central brain nuclei[2], and ventricles. The coarse points were counted over temporal lobe and parietal lobe cortex. For frontal lobe cortex and white matter it suffices to count every fourth (*encircled*) coarse point. To estimate surface, all intercepts crossing the pial surface are counted for occipital and archicortex, while only every second intercept (*test line with encircled end*) is counted for frontal, parietal and temporal lobe

[2] Nucleus caudatus, nucleus lentiformis, claustrum, thalamus, hypothalamic nuclei, nucleus ruber.

Results

Mean volumes are shown in Table 2. The distributions are illustrated in Fig. 2. Cortical thicknesses are shown in Table 3.

Table 2. Stereological estimates of mean volumes (cm^3)

	AIDS group (n = 19)			Controls (n = 19)			Decrease in AIDS	
	cm^3	SD	CV	cm^3	SD	CV	%	$2P$
Neocortex	456	61.6	0.14	510	52	0.10	11	0.01
frontal	197	37.8	0.19	215	32.8	0.15	8	NS
temporal	108	15.4	0.14	120	18.4	0.15	10	0.05
parietal	99	21.0	0.21	117	17.4	0.15	15	0.01
occipital	51	12.4	0.24	58	15.8	0.27	11	NS
Archicortex	41	9.0	0.22	40	8.4	0.21	−4	NS
Central brain nucl.	43	6.0	0.14	52	13.0	0.25	18	0.01
Ventricles	23[a]	–	0.23	15[a]	–	0.34	−55	0.02[b]
White matter	429	54.4	0.13	491	101.8	0.21	13	0.02

[a] Geometric mean

[b] Ignoring the regression

SD, Standard deviation; CV, coefficient of variation; NS, not significant

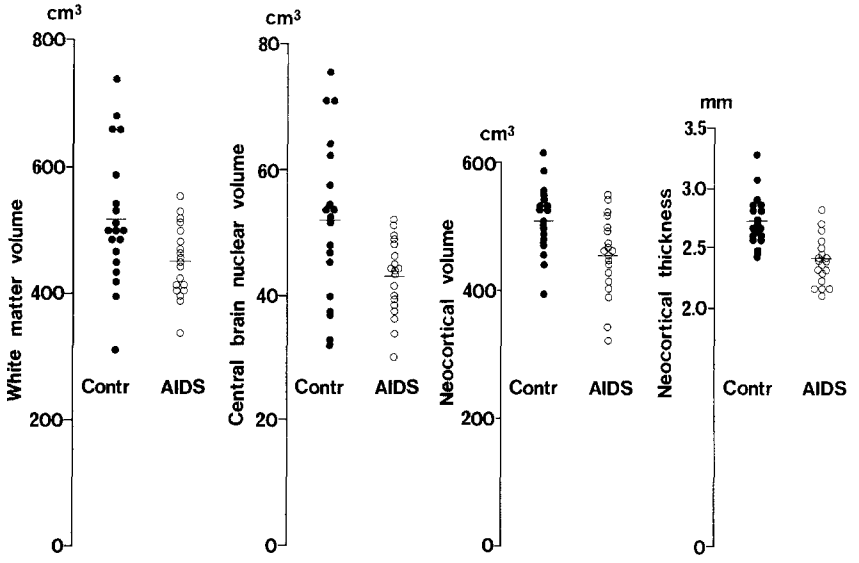

Fig. 2. Distribution of volumes from controls (*filled circles*) and AIDS patients (*open circles*). Note that the spread is less in white matter and central brain nuclei of the AIDS brains

Table 3. Stereological estimates of mean cortical thickness

	AIDS group (n = 19)			Controls (n = 19)			Decrease in AIDS	
	mm	SD	CV	mm	SD	CV	%	$2P$
Neocortex	2.4	0.4	0.08	2.7	0.4	0.08	12	0.001
frontal	2.6	1.0	0.18	3.1	1.0	0.16	15	0.01
temporal	2.4	0.6	0.12	2.8	0.8	0.13	13	0.002
parietal	2.4	0.6	0.11	2.5	0.4	0.10	4	NS
occipital	2.0	0.4	0.11	2.2	0.6	0.12	9	0.05
Archicortex	3.4	1.2	0.17	3.9	2.0	0.26	15	0.025

SD, Standard deviation; CV, coefficient of variation; NS, not significant

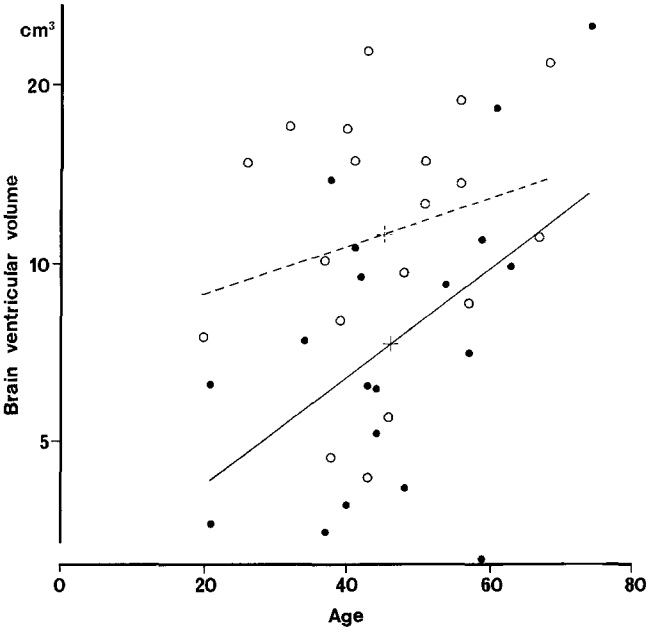

Fig. 3. Ventricular volumes related to age of controls (*filled circles* and *full-drawn line*) and AIDS patients (*open circles* and *dashed line*). The ordinate is logarithmic. Regression lines are shown together with bivariate group mean values (*crossed*). The slopes of the two regression lines differ significantly, $2P < 0.01$

The geometric mean ventricular volume of the AIDS patients was 23 cm³, increased by 55 % from the 15 cm³ of the controls. The ventricular volume was a function of age in controls ($r = 0.51$, $2P = 0.026$), but not significantly so in AIDS patients ($r = 0.24$, $2P > 0.05$). Figure 3 shows ventricular volume related to the age of the patients. The slope of the regression line in controls corresponds to a doubling of ventricular volume every 33 years or an increase of 24 % per decade.

Since the surface area estimates are not unbiased due to cortical anisotropy when sliced in frontal versus horizontal plane, volume and surface areas were estimated on frontal sections of three right and three left hemispheres, and on horizontal sections of the opposite hemispheres. The results are shown in Table 4. There is a fair amount of hemispherical asymmetry in the human brain, as indicated by hemisphere weight and cortical volume when estimated independently of orientation, (see Fig. 4). The relative variation was 4.5 % of hemisphere weight and 7.1 % of cortical volume. There is, however, no indication of consistent asymmetry; the average estimates of right hemispheres deviated less than 1 % from the bilateral means. These estimates of the natural variability provide a yardstick with which to evaluate the biased estimates of cortical surface area.

Table 4. Mean values of six right and six left hemispheres after frontal and horizontal cutting (coefficient of error in parenthesis)

	Frontal	Horizontal
Weight of hemisphere (g)	518	509
	(0.16)	(0.17)
Volume of neocortex (cm^3)	202	208
	(0.13)	(0.17)
Surface of neocortex (cm^2)	825	788
	(0.18)	(0.18)
Neocortical thickness (mm)	2.49	2.65
	(0.11)	(0.05)

Figure 4 also shows the variability of surface area estimates from frontally and horizontally cut hemispheres, and that this is the same as the estimates of natural side variability of weight and cortical volume. The average difference was 2.3 % in cortical surface area when cut frontally vesus horizontally and with a SEM of 2.8 %; this is far from statistical significance. Although estimates of surface area from arbitrarily, non-uniformly oriented sections are always biased, the bias in the estimates of human cortical area is too small to be detectable when compared with the side variability. With the techniques used in this study we, therefore, find it justified to neglect the rather small bias, and for all practical purposes consider the neocortical surface isotropic.

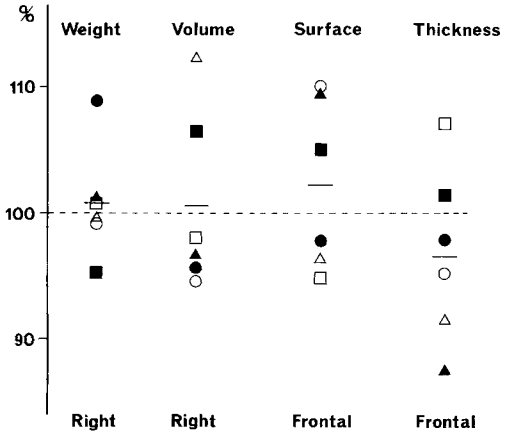

Fig. 4. The relationship between the right and left cerebral hemisphere of six brains that were cut in either the frontal or the horizontal plane. Each symbol represents one brain. *Filled symbols* are used when the right hemisphere is cut frontally and the left horizontally. *Open symbols* are used when the right hemisphere is cut horizontally and the left frontally. *Bars* indicate mean values. *Volume* is the neocortical volume of the right hemisphere in percent of that of the left. *Weight* is the mass of the fixed right hemisphere in percent of that of the left. *Surface* is the area of neocortical pial surface of the frontally cut hemisphere in percent of that of the horizontally cut one. *Thickness* (calculated from volume and surface) represents the neocortical thicknes in the frontally cut hemisphere in percent of that of the horizontally cut one. Note that the surface area and cortical thickness are estimated on non-isotropic slices

Discussion

There was no difference between the mean fixed brain weight of the AIDS patients and the controls, and no correlation between fixed brain weight and cerebral volume.

The mean neocortical volume in the AIDS patients was reduced by 11 %. Atrophy affected all lobes, but was statistically significant only in the temporal and parietal lobes. Central atrophy was more pronounced than cortical atrophy with a 55 % increase in ventricular mean volume and a 18 % reduction in the mean volume of central brain nuclei. White matter was reduced by 13 %.

Our findings probably represent a minimal brain atrophy in a population of AIDS patients since we excluded those that might have other causes for atrophy, especially alcoholics and drug abusers. CT scanning has shown brain atrophy in intravenous drug abusers of a similar degree as in AIDS patients [20].

The stereological procedure is simple and efficient, and permits estimation of volumes of enclosed structures like the central gray matter and white matter. The estimates of volumes and surfaces area in one hemisphere can be obtained in about 2 h. The practical preparations take about 1 h. It does not interfere with further histological examination, even immunohistochemical stains are not adversely affected by embedding in hot agar. The densities of the test system have proved efficient [2], as the coefficient of error of about 5 % cannot be reduced by counting more points. To get a more precise volume of the smallest structures, thinner slices are required.

The results may be influenced to an unknown degree by the volume changes during fixation. This may not be the same in brains from AIDS patients and from controls either as a whole or in different structures (like cortex and white matter), or from one brain to the other. This is a major limitation in interpreting results obtained from fixed brain tissue. At present security precautions do not permit the method to be used on fresh brains from AIDS patients. Embedding in agar itself does not affect the volume [29]. It is, however, not likely that the volume reduction is a mere artifact.

Degenerative changes of myelin are often found. In HIV leukoencephalopathy, in which a reduction in axonal volume and myelin sheath thickness has been described [16], this may explain the white matter atrophy in some cases.

Atrophy, often expressed as an increased ventricle-brain ratio, has been noted more by radiologists than by pathologists, and mostly in demented patients. There was a trend towards more pronounced central atrophy in the six demented patients in this material, but it was not statistically significant.

It is noteworthy that the difference in ventricular volume between patients and controls was more marked in the brains from the younger men (see Fig. 3). A reduced neuronal density has been demonstrated in frontal, temporal and parietal cortex in AIDS brains [6, 9, 17, 34]. Using the disector principle in a non-

uniform design, a reduction in nerve cell density by 38 % was demonstrated in a specified gyrus in the frontal cortex [6]. This does not, by itself, indicate a general cell loss, as the selected gyrus need not be representative for the whole of frontal cortex.

Cortical atrophy could be a result, at least in part, of a decreased total number of neurons. Whether that is the case in general remains to be demonstrated. Studies in progress will show the total number of cells in the different cerebral regions.

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