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Value of volumetric head CT in diagnostics and differentiation of selected dementive disorders

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Summary

Background: Aging of the societies and increasing age expectancy observed in the recent years has resulted in increased incidence of dementive diseases, which are more common in the elderly and cause currently serious diagnostic problems. For this reason, much effort has been focused on the possibility of early detection of dementive disorders, their diagnosis and institution applying of appropriate treatment as soon as possible.

The aim of the study was to assess the value of volumetric head CT in the diagnostics and differentiation of the following dementive disorders: Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia (MD).

Material/Methods: The study was carried out in a group of 78 patients diagnosed with dementia on the basis of clinical classifications (48 with AD, 15 with VaD and 15 with MD) and 15 control subjects. All the patients underwent head CT, followed by volumetric calculations of cortical and subcortical cerebral atrophy with own semi-automatic method. The following parameters were evaluated: cerebrospinal fluid (CSF) volume in the ventricular system, CSF volume in the subarachnoid space in the frontal, temporal and parieto-occipital regions, and the volume of the supratentorial portion of the brain. Then the results were subjected to statistical analysis to detect the differences in these parameters between the patients and controls, as well as among the patient subgroups with AD, VaD and MD.

Results: More advanced atrophic changes were demonstrated in dementia patients in comparison with the control group. Most statistically significant differences were found in the MD group. No significant differences among the dementia subgroups were observed, except for larger amounts of CSF in the temporal area in MD patients in comparison with VaD ones.

Conclusions: CT volumetry is an objective, quantitative method allowing to assess cerebral atrophy in patients with dementia. However, it has a limited value in differentiation of dementia types. CT volumetry used in long-term studies can be particularly useful for monitoring dementia patients and assessment of treatment results.

Key words: CT volumetry • dementive disorders

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Background

In the aging societies, dementive disorders affect an increasing proportion of the general population. With advent of the new methods of pharmaceutical therapy emerging in the recent years, the task of developing early disease marker techniques, which would be sensitive and specific, is becoming more and more important. Neuroimaging has been used for a long time primarily to exclude other, so-called "curable" causes of dementia, e.g. normotensive hydrocephalus, brain tumors, abnormalities of vascular origin or inflammatory processes [1–3].

However, the research conducted in the recent years has been searching for new possibilities of neuroimaging in the diagnostic process of dementive disorders. One of such possibilities is assessment of atrophic changes in the brain and the progression of such changes in the course of the disease,

Table 1. General characteristics of the patient groups.

Characteristics	AD	VaD	MD	All patients with dementia	CG (control group)
Number	48	15	15	78	15
Age (years)	45–88 mean 71.3	45–92 mean 66.4	50–84 mean 69.4	40–72 mean 70	46–80 śr. 62
Gender (F, M)	33F, 15M	12F, 3 M	13F, 2M	55F, 23M	5F, 10M
Education level E – elementary S – secondary A – academic	 12E 24 S 6 A	 10E 3 S 2 A	 4 E 10 S 1 A	 23 E 37 S 9 A	No information available
MMSE (score)	0–23, mean 16.6	12–23, mean 19.1	10–23 mean 16.9	0–23 śr. 17.5	No data
Clock test (level)	I–IV, mean. II	I–III mean. II	I–III mean. II/III	I–IV mean. II	No data

as well as attempts of determination whether increased extent of atrophic changes may suggest the onset of neurodegenerative ones and development of a dementive disorder and whether the location of atrophic changes is typical of a particular dementia form.

The authors focused their attention on the applicability of volumetry based on CT, which is most available and performed as the first-line examination in the imaging diagnostics algorithm used in dementive patients. Other known advantages of CT include: short duration (important in patients with symptoms of dementia who are difficult to cooperate with), possibility to repeat the scans in case of movement artifacts, as well as possibility to perform the examination in subjects with contraindications for MR (e.g. with cardiac pacemakers or suffering from claustrophobia). Apart from that, CT is associated with much lower costs and full monitoring of the patients is possible in CT laboratories.

Aim of the study

The aim of the study was to assess the value of volumetric head CT in the diagnostics and differentiation of the following dementive disorders: Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia (MD), by realization of the following objectives: development of own semi-automatic method of volumetry, comparison of volumetry results between the patient group and the control subjects and comparison of the results among the subgroups of dementive patients.

Material and Methods

The studied material consisted of 78 patients diagnosed with dementive syndromes treated in the Department of Psychiatry of the Wrocław Medical University and 15 control subjects who underwent head CT in 2004–2007.

The patient group consisted of 58 women and 20 men aged from 40 to 92 years (mean age 70), diagnosed on the basis of applicable clinical classifications with dementive disorders: Alzheimer's disease (AD) – 48 patients, vascular dementia (VaD) – 15 patients and mixed dementia (MD) 15 patients (Table 1).

The diagnoses of AD and VaD were based on ICD-10 and DSM-IV classifications supplemented with NINCDS-ADRDA criteria in case of AD and NINDS-AIREN for VaD. The diagnosis of MD, for which no commonly accepted classifications are available, was established on the basis of anamnesis and clinical presentation in patients who did not meet the diagnostic criteria either for pure AD and VaD, or for any other dementive disorders.

The control group was formed retrospectively from patients who had undergone CT for diagnostics of headaches, whose clinical information available in referral forms did not include cognitive function impairment or signs of focal deficits.

Computed tomography was performed on a two-row CT scanner (Dual HiSpeed, GE) using a standard sequential technique head scanning program. The images were first subjected to visual assessment to exclude organic etiology of cognitive function impairment. The technical parameters of data acquisition are presented in the table (Table 2).

Source images were transferred to a Magic View 1000 diagnostic unit for processing, based on own method combining automatic calculation of voxels' volume within the density range including that of cerebrospinal fluid (–10 to +25 HU) with optional correction of the areas marked by the program by manual delineation in the particular layers of conventional CT scans (Figure 1). The following parameters were assessed: cerebrospinal fluid (CSF) volume in the subarachnoid spaces and basal cisterns (generalized cortical atrophy) and separately for frontal, temporal and parieto-occipital regions, as well as CSF volume in the ventricular system (in the supratentorial space and in the IV ventricle – subcortical atrophy) (Figures 1,2).

Results

The analysis of the results involved comparison of the mean CSF volume values obtained from the regions of interest

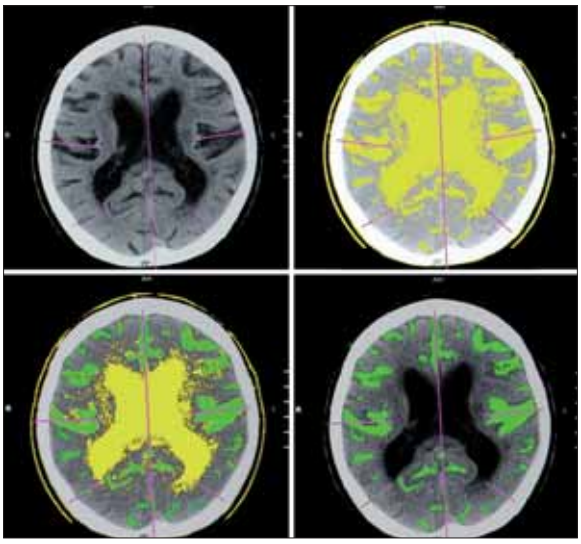

Figure 1. Assessment of cortical atrophy – areas containing CSF, marked automatically by the program (yellow); with manual marking of the CNS in cerebral sulci (green).

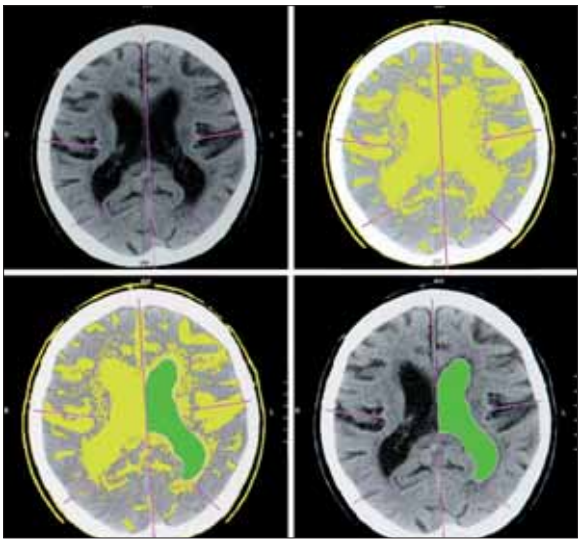

Figure 2. Assessment of subcortical atrophy – areas containing CSF, marked automatically by the program (yellow); with outline of the left lateral ventricle plotted manually (green).

Table 2. Technical parameters of data acquisition on head CT.

Parameters	Head CT
Voltage	120 kV
Current	130 mA
Scanning time	ca. 24 s
Slice thickness	7 mm in supratentorial space 4 mm posterior cranial fossa
Gantry angle	Parallel to the orbital vault
Scope	From the foramen magnum to the calvaria
Field of vision (FOV) size	20–25 cm
Number of scans	ca. 18

(ROI) between the whole group of dementive patients and the control group (CG), AD, VaD and MD subgroups and the control group, as well as among AD, VaD and MD patient groups.

Statistically significant intergroup differences ($p<0.05$) in the volumes of CSF around the whole supratentorial portion of the brain (providing indirect evidence of generalized cortical atrophy) were found only between MD and CG subjects.

Significantly larger volume of the supratentorial ventricular system (suggesting subcortical atrophy) in comparison with the control group was demonstrated in AD and MD patients, but the difference was most pronounced for the AD group (statistical significance at 0.1% confidence level). A statistically significant difference in the volume of supratentorial ventricular system was observed when the whole dementive patient group (study group, SG) was compared with the control group (CG) ($p<0,01$). No statistically significant difference in supratentorial ventricular system volumes was demonstrated between patients with vascular dementia (VaD) and CG patients.

Comparison of the mean IV ventricle volume between the dementia groups and the control group revealed that it was significantly larger in all three groups of dementive patients, as well as in the whole dementive patient group.

Analysis of the mean CSF volumes in the temporal region demonstrated statistically significant differences between MD and CG patients.

No statistically significant differences in CSF volume around the frontal lobes were found either among dementive patient subgroups, or between the particular dementia groups and the control group, or between all dementive patients and the control group.

Significantly larger CSF volumes in the parieto-occipital regions in comparison with CG were demonstrated in patients with Alzheimer's disease (AD) and mixed dementia (MD). Vascular dementia (VaD) patients and the whole study group (SG) demonstrated no statistically significant differences in comparison with the control group.

Table 3 presents the comparison of mean CSF volumes between dementia patient subgroups and the control group.

The next stage involved comparison of CSF volumes in the aforementioned regions of interest among the subgroups of dementia patients (Table 4).

The only difference between patient subgroups reaching statistical significance ($p<0.05$) were found for MD and VaD with respect to increased CSF volume in the temporal region. However, no statistically significant differences in CSF volumes between either AD and VaD or AD and MD were demonstrated for other regions of interest.

Table 3. Comparison of mean CSF volumes between dementia patients and controls (Student-t test).

Region	SG vs. CG	AD vs. CG	MD vs. CG	VaD vs. CG
Temporal	–	–	2.26*	–
Frontal	–	–	–	–
Parieto-occipital	–	2.04*	2.15*	–
Generalized cortical atrophy	–	–	2.14*	–
Supratentorial ventricular system	3.01**	3.77***	2.63*	–
IV ventricle	2.38*	2.01*	2.81**	2.59*

* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Discussion

On the basis of neuropathological studies, 3 main stages have been distinguished in the course of Alzheimer's disease (AD). At the first one, usually asymptomatic, morphological changes are detected selectively in perihippocampal areas (hippocampal gyri and enthorhinal cortex). At the subsequent stage, the degenerative process involves additionally the structures of the medial part of the temporal lobe and the limbic system, with the hippocampal system affected in particular. At the last stage, the pathologic changes spread to the remaining areas of the cerebral cortex, involving extensive cortex portions of the temporal, parietal and frontal lobes [4–7].

The results of imaging studies conducted and published to date seem to correlate with the described pathologic changes. Studies of patients with mild cognitive impairment (MCI) demonstrated reduced volume of the parahippocampal gyrus, which suggests atrophic changes of degenerative origin, associated probably with the earliest morphological changes described at the preclinical stage of Alzheimer's disease [8].

The results confirming volume loss in the structures located in the medial portion of the temporal lobe, primarily the enthorhinal cortex (ERC) and the hippocampus in AD patients have been obtained in volumetric studies, based mainly on MR imaging [9–11].

Longitudinal studies, in which the investigators' attention was focused mainly on the type character and location of atrophic changes developed in the course of the disease, were also conducted. The results indicated progressive atrophy both in the ERC and in the hippocampus [12–14].

The results of CSF imaging in the temporal regions of patients with AD and in the control group, obtained by the authors, did not demonstrate statistically significant differences. The failure to demonstrate significant volume reduction of the temporal lobes, reported by other authors, is probably due to the adopted calculation methodology. In this study, the assessment of CSF-filled space volume in the temporal areas included the brain sections above the level of petrous pyramid apices in order to avoid calculation errors due to artifacts caused by bones of the skull base. A possibility of additional temporal lobe scans performed after standard CT of the head in the plane parallel to the lobe longitudinal axis, proposed previously by other authors, was also considered [15–18]. Eventually, it was decided to assess the utility of volumetry which can be based on standard, routine CT, without modifications and additional exposure of the patients to radiation.

Table 4. Comparison of mean CSF volumes among dementia subgroups (Student-t test).

Region	AD vs. VaD	AD vs. MD	MD vs. VaD
Temporal	–	–	2.293*
Frontal	–	–	–
Parieto-occipital	–	–	–
Generalized cortical atrophy	–	–	–
Supratentorial ventricular system	–	–	–
IV ventricle	–	–	–

* $p<0.05$.

Another ROI assessed was the region of the frontal lobes. Despite diffuse pattern character of cortical atrophy in advanced AD, mentioned above, the authors did not find any publications describing statistically significant differences in frontal lobe volume in comparison with control subjects. No such differences have been demonstrated on the basis of this study, either. The available publications describe rather absence of advanced atrophic changes in the frontal regions in AD patients, which is useful in differential diagnostics of patients with fronto-temporal dementia (FTD), in view of considerable similarity and overlapping of clinical symptoms between these two groups of patients [19]. A longitudinal study comparing the extent of atrophic changes over time in AD and FTD patients demonstrated in the FTD group more rapid progression of atrophic changes, limited primarily to the frontal areas, whereas slower progression of atrophic changes with more diffused pattern in character was observed in AD patients [20].

There are few reports concerning structural changes in the parietal regions in AD patients. The changes in that region described in AD most often concern blood flow disturbances detected by functional imaging modalities, primarily SPECT [21–23]. Structural changes in this region were described by Du et al., who measured the thickness of the cerebral cortex in AD patients and found it to be thinned in the parietal, temporal and occipital regions [24]. The analyzed AD group also demonstrated significantly increased CSF volume in the parieto-occipital region in comparison with the control subjects, which may indicate indirectly cortical atrophy

in this area. In order to avoid measurement errors due to artifacts caused by the cranial calvaria bones, no measurements were performed on the scans acquired at the levels just below the calvaria.

In the authors' opinion, the results suggestive of atrophic changes in the parieto-occipital region in AD patients may result from the degree of cognitive impairment in the analyzed group. The mean MMSE score obtained in these patients was 16, which corresponds to moderately advanced disease, characterized by the stage of cortical deficits consistent with the neuropathological classification mentioned at the beginning of the paper.

The literature reports also significantly larger volumes of the ventricular system in AD patients in comparison with control subjects. Such results provide indirect evidence of subcortical atrophy. The authors who published those results performed measurements, both planimetric and volumetric, based on CT imaging in cross-sectional and prospective studies [25–27]. Significantly increased ventricular system volume was also demonstrated in volumetric studies based on MR imaging [28–31].

In our study, comparison of the ventricular system volumes in AD patients and CG also confirmed its larger volume in the AD group, which suggests subcortical atrophy.

Another analyzed group were VaD patients. The causes of cognitive function disturbances in case of subcortical atrophy of vascular etiology still remain unclear. They are supposed to result directly from the presence of lacunar infarcts and lesions of the white matter, which are responsible for damage to important cortico-subcortical pathways.

A study assessing cognitive impairment severity in subjects with lacunar infarcts demonstrated a correlation between progression of dementive disorders with the volumes of the hippocampus and the gray matter. Interestingly, the study failed to demonstrate any correlation between the severity of cognitive impairment any measurement of lacunar infarct size. Additionally, hippocampal and cortical atrophy were found to be partially independent in VaD patients, which resulted in a hypothesis that hippocampal atrophy in this group may be associated with the coincidence of neurodegenerative and ischemic changes, whereas cortical atrophy can correlate with changes in the white matter [32,33].

The analyzed material did not demonstrate statistically significant differences of the CSF volume in the ROI assessed, except for the volume of the IV ventricle, between VAD patients and CG.

In the authors' opinion, such results may suggest that atrophic changes taking place in the course of vascular dementia do not differ significantly from physiological aging of the brain, and cognitive impairment results primarily from the presence of vascular abnormalities, which have no influence on cortical or subcortical atrophy. On the other hand, small size of the group and the fact that mean score obtained in the neuropsychological MMSE test in the VaD group was 19.1, which indicates mild dementia, should be taken into consideration. It seems highly probable that no secondary atrophic changes can be detected yet at this stage.

The last analyzed subgroup consisted of patients with mixed dementia, qualified to this group on the basis of clinical examination and neuropsychological test results.

The diagnosis of MD is a controversial issue. Some authors note high frequency of abnormalities of vascular origin, such as leukoaraiosis areas and small lacunar lesions in patients with provisional diagnosis of AD, which in their opinion suggests too rare diagnoses of the mixed form of cognitive impairment [34–36]. Other authors claim that there are only AD forms with vascular lesion components and VaD with coincident degenerative changes [37,38].

In a study carried out by Whitwell et al. in a group of patients with dementia diagnosed on the basis of histopathology, higher annual progression rates of cerebral atrophy and enlargement of the ventricular system were demonstrated in MD patients in comparison with the control group [39].

Some authors observed larger extent of cortical and subcortical atrophy in the temporal regions of patients with MD in comparison with healthy controls. Diffuse lesions with decreased radiation attenuation coefficient within the white matter of the frontal region and small, lacunar focal lesions were also observed in MD patients [35].

Most statistically significant differences from the control group were observed in the analyzed MD patients: larger extent of generalized cortical atrophy, and on analysis of the particular ROIs larger extent of atrophy in both temporal and parieto-occipital areas. Additionally, MD patients presented large volumes of the ventricular systems than patients without cognitive impairment.

The overall spectrum of the obtained results suggests the presence of most complex neurodegenerative changes in this form of cognitive function disturbances. Also the fact of larger atrophy extent found in the temporal lobes of MD patients in comparison with CG, which was not found in the AD group (as mentioned above, probably because of the adopted research methodology). Such results may suggest that in MD neurodegenerative changes involve the upper portions of the temporal lobes in contrast to AD, where the changes in medial portions of these lobes are described. However, because of small size of the groups, further research is necessary to verify this hypothesis.

Publications concerning comparisons of volumetry results obtained in various forms of dementive disorders are scarce and describe primarily MR-based calculations.

In a study assessing the total cerebral volume, CSF and separately the volumes of the temporal, frontal, parietal lobes, cerebellum and the hippocampus-amygdala complex, Pantel et al. demonstrated no significant differences in the volumes of brain structures and CSF-filled spaces in the supratentorial area between AD and VaD patient groups; the only difference that reached statistical significance was observed for the cerebellum. The cited authors formulat-

ed a hypothesis based on similar distribution of atrophic changes, that the atrophic deficit site is not dependent on the pathogenesis of brain damage, but rather on specific sensitivity of neuroanatomical structures [40].

Varma et al., assessing cerebral atrophy and functional impairment in AD and VaD patients found more pronounced atrophic changes in the parietal region, with parallel decrease of cerebral flow parameters in SPECT, in AD patients, whereas in the VaD group atrophic changes in the brain were found only sporadically [23].

Comparing patients with AD, dementia with Lewy's bodies (DLB), VaD and age-matched controls without cognitive impairment, Barber et al. observed larger volumes of the temporal lobe, hippocampus and amygdaloid nucleus in the patients with VaD and DLB than in those with AD, with no statistically significant differences between the VaD and DLB groups. The study demonstrated also larger ventricular system volume in all dementia patients in comparison with healthy controls and no differences in frontal lobe volume among the dementia subgroups [41].

As demonstrated in longitudinal studies by Mungas et al., progression of cortical atrophy is associated with the prognosis of cognitive function deterioration and more rapid progression of the disease, which means that it can be treated as an indicator of the stage of the disease both in AD and in VaD patients. An additional correlation between hippocampal atrophy progression and deterioration of cognitive function was found in AD patients. No such correlation could be demonstrated in the VaD group, which, according to the authors, suggests different etiology of these pathologies [42].

Results of studies comparing AD and MD patients are scarce. Hsu et al. observed that in patients diagnosed with AD and lacunar lesions present in the brain (who can be treated as an MD group), white matter lesions and the ventricular system are found to have larger volume, with reduced volume of the CSF present in the cerebral sulci in comparison with the group without lacunar lesions. The authors conclude that the presence of lacunar lesions in the brain may influence the changes of ventricular system volume (subcortical atrophy), whereas it demonstrates no correlations with cortical atrophy [43].

Whitwell et al., in a study carried out in a group of AD and MD patients diagnosed on the basis of histopathology, demonstrated a higher annual progression rate of cortical atrophy and enlargement of the ventricular system in comparison with the control group. No significant differences in cortical and subcortical atrophy grades in AD and MD patients were demonstrated (like in our study) [39].

In our study, the comparison of volumetric calculations in patients in the particular dementia groups failed to demonstrate statistically significant differences between AD and VaD and between AD and MD.

On the other hand, statistical analysis demonstrated statistically significant differences between the VaD and MD subgroups, such as larger volume of CSF in the left temporal region in MD patients. These results suggest greater extent of cortical atrophy in mixed dementia.

Conclusions

1. The results of CT volumetry are to a large extent consistent with the results of similar volumetric studies reported by other authors.

2. Dementive patients in AD and MD subgroups demonstrate significant differences in the volume of intracranial structures and fluid-filled spaces in comparison with the control group.

3. Most differences reaching statistical significance (including more pronounced temporal lobe atrophy as compared with the control group and VaD patients) were observed in the MD group, which may confirm the most complex character of the pathology.

4. In doubtful cases, CT volumetry could assist differentiation between VaD and MD patients on the basis of more pronounced atrophic changes in the temporal lobes in MD; however, the reliability of this finding requires confirmation in larger patient groups and in longitudinal studies.

5. The lack of differences between the VaD and control groups may confirm the thesis that in this group of patients cognitive function impairment is due to changes in the white matter rather than to atrophy of the gray matter.

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