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Application of own computer program for assessment of brain-fluid index in the medial temporal lobe portions in patients with drug-resistant temporal lobe epilepsy

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Summary

Background: Epilepsy resistant to pharmacological treatment still remains one of the main problems in contemporary epileptology. The problem most frequently concerns patients with focal epilepsy, with the seizure focus possible to localize. In case of drug-resistant epilepsy, both morphological imaging methods (MR) and manual measurementa or volumetry are used. Also functional studies, such as MRS (magnetic resonance spectroscopy), fMRI (functional magnetic resonance), SPECT (single photon emission tomography) and PET (positron emission tomography) are performed.

Material/Methods: The study presents application of own computer program based on the method of segmentation of the cerebrospinal fluid (CSF) and the brain tissue. The program calculates automatically the brain-fluin index in the hippocampal region. The material comprises the brain-fluin index results calculated with the presented program in comparison with the method of manual delineation in a group of 50 patients with drug-resistant temporal lobe epilepsy. The program is easy to use, it reads the MR data recorded in DICOM installed on a PC.

Results: The brain-fluin index result (expressed as a decimal fraction) is calculated on the basis of 4 consecutive layers examined by MR (evaluating hippocampal structures) performed using SE sequence, and T2-weighted imaging in the frontal plane perpendicular to the long axis of the temporal lobes. The results obtained in epilepsy patients were compared with 24 control subjects.

Conclusions: Detailed analysis of the obtained data allowed to conclude that precise hippocampal volume assessment can be obtained by combination of both methods, i.e. manual delineation and automatic calculation of brain-fluin index taking into consideration the total volume of cerebral structures.

Key words: temporal lobe epilepsy • manual measurement methods • volumetric methods • MRS (magnetic resonance spectroscopy)

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Background

Failures to obtain complete control of seizures with optimal pharmacological treatment in ca. 30% of epilepsy patients [1] lead to increasing interest in surgical methods giving a chance of elimination, or effective reduction in the frequency and severity of seizures and consequent improvement of the patients' quality of life [2]. In preoperative diagnostics, effective methods are sought which would allow precise delineation of the epileptogenesis zones and localization of the eloquent telencephalic areas whose damage could result in cognitive or motor function deficits [3].

Magnetic resonance imaging (MRI) is the most important imaging modality visualizing the brain, which allows to detect even subtle focal structural anomalies observed in temporal lobe epilepsy: cortical dysplasia foci, benign DNET (Dysembrioplastic Neuroepithelial/Neuroectodermal Tumor) or ganglioglioma type tumors or other dysplastic lesions even at early stages of development, cavernous angiomas, or other vascular malformations, cortico-subcortical scarring or mesial temporal sclerosis (MTS).

In comparison with CT, the sensitivity of MR is inferior with respect to detection of microcalcifications only.

The commonly used visual assessment of standard MR results can, however, be unreliable even if done by a radiologist with extensive experience in imaging of cerebral structures [4].

In preoperative diagnostics of epileptic foci, video-EEG, sometimes performed by means of intracranially implanted electrodes, allowing neurophysiological localization of the focus based on assessment of the semiology of seizures and sites of their origin, plays an important role. Functional neuroimaging modalities such as fMRI (functional magnetic resonance), EEG-triggered fMRI, SPECT (single photon emission tomography), SISCOM with subtraction of SPECT images obtained by comparison of scans performed in seizure-free period and at the beginning of a seizure, with the subtraction result superimposed on MR images, and PET (positron emission tomography) performed in seizure-free period, mainly with assessment of glucose utilization (FDG) and benzodiazepine receptors (FMZ) [5].

On the basis of economic considerations, thorough analysis of images obtained by standard MR before extending the diagnostics by complex functional studies has been recommended.

The role of volumetric assessment based on standard MR of the brain in localization of epileptic foci has not been determined unequivocally. Therefore, it was attempted to compare the value of volumetric assessment of the medial temporal lobe portions by manual delineation and by means of an own, semi-automatic method allowing to calculate the brain-fluin index in the region of interest (ROI).

Material and Methods

MR images of the brain obtained from 50 patients (16 men and 34 women mean age 35.9 SD=13.6) with focal temporal lobe epilepsy resistant to pharmacological treatment were analyzed thoroughly.

Normal values for the methods applied were calculated on the basis of MR performed in the control group of 24 healthy subjects: 12 men and 12 women (mean age 33.0 SD=9.9).

The temporal lobes were evaluated with the following methods to make radiological assessment more objective:
1. manual delineation of medial temporal lobe structures;
2. own computer program calculating the brain-fluin index automatically.

MR was performed with PROVIEV equipment (MARCONI, now Philips) of 0.23T field intensity using SE sequence, and T2-weighted imaging in the frontal plane perpendicular to the long axis of the temporal lobes.

Ad 1. Manual measurement of the temporal lobe was performed using an Omni Pro console with 3D program utilizing T2-weighted MR images obtained in SE sequence in sagittal plane with layer thickness of 3 mm.

The external contours of the hippocampus were delineated on the consecutive layers, eventually calculating the volume of this anatomic structure as the product of summary surface areas and layer thickness according to the following formula:

$$Vt = Sc \times d$$

$$St = S1 + S2 + \ldots\ldots + Sn$$

Vt – total volume;

St – total surface area;

S1… Sn – surface areas of individual layers.

Using an appropriate automatic program, the delineated surfaces from all selected layers are summed up and after clicking the „finish" command the total volume is given.

Analogical measurements were performed for the contralateral cerebral hemisphere.

Ad 2. Description of the own program for hippocampal brain-fluin index.

The program was based on freeware DICOM files viewer package – ArPACS. The carrier (CDROM) must contain a DICOMDIR file, constituting a kind of database in the DICOM standard. The HypoCamp program accepts CDROMs generated by most manufacturers of diagnostic equipment. After introducing the carrier, the user has to select one of brain MR imaging series.

The first stage of the measurement involves determination of the intracranial transversal dimension (so-called normalization line), taking into consideration the differences in cerebral volumes of the examined patients (Figure 1A).

With ROI1, a cerebral site of 100 mm^2 area should be selected to determine the mean value and standard deviation of pixel density (Figure 1B). Then, ROI2 (of 600 mm^2 area)

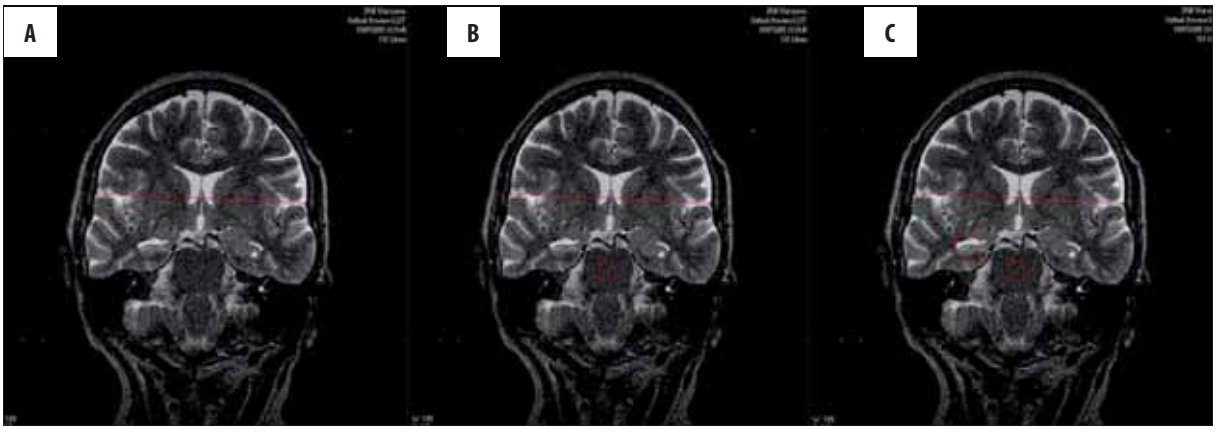

Figure 1A–C. The consecutive steps of measurement are presented: intracranial transversal dimension (Dim) determination (**A**), setting ROI 1, i.e. the reference site for pixel density (**B**), setting ROI 2, i.e. the proper measurement area for brain liquor space index calculation (**C**).

should be placed at the location where the pixels will be counted, i.e. covering the hippocampal structures together with the inferior horn of the lateral ventricle (Figure 1C).

All the settings described above are performed only once, on the first of four MR layers selected for assessment. As they are transferred automatically to the other layers. If the measurement is correct, it can be recorded as a text file by clicking "Save".

The data introduced to the program are obtained by MR imaging of the cerebral structures. The computer coupled with the MR unit, after collection of data from the receiver tubes, generates an image within a matrix (usually 256×256), with single pixel value ranging usually from 0 to 4095 (12 depth). The standard deviation value is determined on the basis of definitions for non-continuous (discrete) distributions as a square root of variance normalized to the number of the counted pixels; (variance = Sum (pixel(s) value – mean value), where „s" corresponds to the range from 1 to the number of pixels in ROI). If the standard deviation in the selected area is high, it may indicate a high proportion of noise in the image or unclear tissue differentiation in the ROI.

In such a case, it should be checked (by changing the **imaging window**), whether there are tissues other than expected in the selected ROI.

The results saved as a file make it possible to perform complex calculations and to compare the results of different patients using any calculation software (e.g. MathLab, Calc or Excel).

The accuracy of estimated area surface (the value determining measurement accuracy) depends on the accuracy of diagnostic equipment used, as well as on care taken during data collection and processing with HypoCamp program.

Results

Statistical calculations were performed to assess:

1. Statistical significance of the observed differences between the patients and the control group (Studenta-t test for independent samples was used). The adopted significance level was $\alpha = 0.05$ ($p < \alpha \Rightarrow$ Ho-)

$$p < 0.05.$$

2. Sensitivity and specificity of the used diagnostic technique (matrix calculation was used for this purpose).

The distinguished groups – the studied group of epilepsy patients and the control subjects (denoted as EPI and CONTR) – were found to differ significantly in the mean values of the Man parameter (hippocampal volume index calculated in MR – with pooled values for the right and left side):

Group	Mean	STD
EPI	1437.1	455.1
CONTR	2782.1	509.0

It was established that the mean values differed with statistical significance. (Student-t test, statistics value $t = -15.75$, $p < 0.0001$).

The significance of differences between the mean values of the Ind parameter – defined as a ratio of the surface area (and volume approximated on that basis) of the fluid to neural tissue on axial sections at the brain stem level) in the patient and control group (EPI and CONTR) was assessed separately. The observed differences between these groups were found to remain on the threshold of the adopted statistical significance (Student-t test, statistics value $t = 1.57$, $p = 0.0597$).

It was attempted to distinguish the groups on the basis of the measured values.

The following 5 criteria, which were analyzed separately, were adopted:

1. For both hemispheres Man higher than/equal to 2000 (implies) ⇒ CONTR, lower for at least one hemisphere ⇒ EPI.
2. For both hemispheres Man higher than/equal to 2200 ⇒ CONTR, lower for at least one hemisphere ⇒ EPI.

3. For at least one hemisphere Ind higher than/equal to 0.1250 ⇒ EPI, lower for both hemispheres ⇒ CONTR.
4. For both hemispheres Man higher than/equal to 2000 ⇒ CONTR, lower for at least one hemisphere ⇒ EPI, or Ind for at least one hemisphere higher than/equal to 0.1250 ⇒ EPI, lower for both hemispheres ⇒ CONTR.
5. For both hemispheres Man higher than/equal to 2200 ⇒ CONTR, lower for at least one hemisphere ⇒ EPI or Ind for at least one hemisphere higher than/equal to 0.1250 ⇒ EPI, lower for both hemispheres ⇒ CONTR.

Contingence matrixes were defined for each of these criteria.

Then, standard indexes expressing sensitivity and specificity of the evaluated method and its positive and negative predictive value (expressed as per cent) were calculated:

Index	Crit. 1	Crit. 2	Crit. 3	Crit. 4	Crit. 5
Sensitivity	92.2%	100.0%	41.2%	94.1%	100.0%
Specificity	90.9%	81.8%	81.8%	72.7%	63.6%
Pos. pred. value	95.9%	92.7%	88.0%	88.9%	86.4%
Neg. pred. value	83.3%	100.0%	37.5%	84.2%	100.0%

It can be noticed that the criterion associated with the Index is weaker than the volumetric one and its contribution is small when both are analyzed together.

It is also notable that improvement of sensitivity in criterion 2 is achieved at the cost of marked deterioration of specificity. To eliminate this disadvantage, the volumetric parameter was defined in a different way, expressing it as a relative index associated with individual cranial dimensions of each patient.

A new Ind 3, defined as a measure of tissue volume corrected for the internal cranial dimensions at the level of the analyzed axial section was calculated.

As direct measurement of cranial volume is not available, but only its wisdth in the particular section (Dim), therefore, to construe a parameter serving as a conventional measure of individual cranial volume of each patient (although failing to express its physical value) – third power of Dim (divided by third power of 100 to maintain the measure similarity to Dim) was adopted as the approximetion of the measure of cranial volume. Thus:

$$\text{Ind 3} = \text{Man} \times \%\,\text{tis} \times 100^3 / \text{Dim}^3$$

(where Man – manual measurement result, tis –tissue, i.e. result of determination of%tis = 1 divided by 1+ Ind, Dim – transversal internal dimension of the cranium).

Like both previous indexes, this one is always determined separately for both hemispheres.

It should be emphasized that the index is not a physical measurement of cranial volume (expressed, e.g. in cm^3). It is only a mathematical construction which approximates the cranial volume, serving as its measure and reflecting the individual characteristics of each patient in this respect.

For the index calculated in this way, the following criterion was adopted (#):

(#) If at least in one hemisphere the Ind 3 parameter is lower than/equal to 905, ⇒ the patient belongs to the study group (EPI), and not to the control group. Otherwise, he/she belongs, by definition, to the control group (CONTR).

The parameter defined in such a way was found to provide satisfactory differentiation between the groups. The mean Ind 3 values for EPI and CONTR differ significantly – Student-t test, statistics value $t = -15.95$, $p = 0.0001$.

An appropriate contingency matrix and appropriate indexes were calculated for the criterion:

Index	Criterion (#)
Sensitivity	98.0%
Specificity	100.0%
Pos. pred. value	100.0%
Neg. pred. value	95.7%

Statistical analysis allows to conclude that the parameter construed in this way differentiates between both groups in the best of the ways tested in the aspect of practical diagnostic applicability.

Discussion

Morphometry is especially useful for detection of hippocampal asymmetry due to unilateral mass loss caused by atrophy in the course of mesial temporal sclerosis (MTS). Such mass (volume) defects can include other structures of the temporal lobe and the rhinencephalon and are usually markers of the side affected by epileptogenesis.

Bonilha et al. [6] based their morphometric studies on T1-weighted images. The olfactory cortex, lateral and medial temporal regions, both hippocampuses and amygdaloid bodies were investigated. Patients with both right- and left-sided temporal lobe epilepsy were demonstrated to have significantly reduced volume of the olfactory cortex ipsilateral to the atrophic hippocampus in comparison with the control group. Additionally, patients with right-sided epilepsy had markedly reduced volumes of all the investigated structures on the right side in comparison with those with left-sided epilepsy. These results are somewhat contradictory to the later studies by the same authors [7].

They investigated the asymmetry of temporal lobe cortical layer atrophy (excluding the hippocampus) in patients with drug-resistant temporal lobe epilepsy using morphometric analysis. In left-sided epilepsy group, hippocampal atrophy correlated to a larger extent with gray matter defects in the parahippocampal gyruses than in right-sided epilepsy patients.

The same authors observed in a study of 36 patients with drug-resistant temporal lobe epilepsy that longer duration of the disease correlated with larger extent of hippocampal and parahippocampal atrophy, which may depend on seizure activity. The authors claim that early institution of anticonvulsant treatment may prevent later cerebral atrophy in these patients.

Duzel et al. [8] demonstrated by morphometry in a group of 16 patients that hippocampal volume reduction in MTS closely correlates with limbic system atrophy, affecting the ipsilateral parahippocampal gyrus, callosal gyrus, periorbital areas, thalamus and insula. However, in some cases contralateral lesions were also found.

Bonilha et al. [9] demonstrated by morphometry in 43 patients with drug-resistant temporal lobe epilepsy decreased gray matter concentration within the hippiocampus and perihippocampal areas, thalamus, caudate nucleus, cerebellum, brain stem and parieto-occipital regions. They used a morphometric method to investigate gray matter concentration within the particular thalamic nuclei in 43 patients with primarily unilateral drug-resistant temporal lobe epilepsy. Atrophy was found mainly in the anterior portion of the thalamus, closely related to the limbic hippocampus.

Volumetric studies of 34 temporal lobe epilepsy patients by Seidenberg et al. [10] demonstrated hippocampal volume reduction to correlate with ipsilateral temporal lobe white matter atrophy and bilateral atrophy of white matter in the frontal and parietal lobes. The lesion severity correlated closely with duration of the disease.

A study by Keller et al. [11] of a large group of temporal lobe epilepsy patients (116 subjects) compared two quantitative assessment methods; morphometry for assessment of gray matter concentration and stereological method (Cavalieri) for volume assessment. A significant decrease of gray matter volume and concentration was demonstrated within the hippocampus which had probably been the primary site of epileptic activity. In patients with history of fever-induced convulsions in childhood, hippocampal volume at the affected side was found to be markedly reduced in comparison with patients without such history. Lower concentration of gray matter in the thalamuses, prefrontal gyruses and cerebellum correlated closely with the duration of the disease. The same authors [12] compared standard and optimized morphometric method in patients with temporal lobe epilepsy. They suggest that the use of optimized morphometric method for gray matter evaluation in other neurological disorders may allow to detect discrete changes impossible to identify with standard analysis of gray matter concentration.

Single voxel proton spectroscopy (1H MRS), a non-invasive brain tissue investigation method, is becoming more and more commonly available. This technique, introduced in the 1990's, allows to determine the levels of chemical compounds and ratios of the particular metabolites, making it possible to diagnose and differentiate pathologic foci. Many literature reports concern the application of proton spectroscopy in identification of epileptogenetic foci, which can be very important especially in patients with no detected abnormalities in morphological MR imaging.

Capizziano et al. [13] demonstrated significant NAA depression of the NAA bands and a decrease of NAA/Ch and NAA/Cr ratios in a group of 15 patients with hippocampal sclerosis, confirmed by postoperative histopathology. In 12 of them, MR revealed hippocampal atrophy, whereas in 3 no morphological changes were detected. In all the patients, 1HMRS demonstrated correct lateralization of the epileptic focus, revealing additionally similar metabolite ratios also in the frontal, parietal and occipital lobes ipsilateral to the effected hippocampus.

Similar results, depression of the NAA bands and a decrease of NAA/Cho and NAA/Cr ratios were obtained by Lee SK. et al. [14] in 41 temporal lobe epilepsy patients with normal hippocampal images in FLAIR sequence and t2-weighted images.

Correct localization of epileptogenetic foci was obtained in 65.9% of the studied group, which the authors explain with too large size of the investigated area (voxel) in relation to small size of the pathologic focus. Meiners et al. [15] demonstrated in 11 with histologically confirmed hippocampal sclerosis a significant decrease of NAA/Cho and NAA/Cr ratios in the white matter of the temporal lobe ipsilateral to the affected hippocampus in comparison with the contralateral one and with healthy controls. The results indicate reduced number of axons in the epileptogenetic focus, accompanied by decreased myelin density. Additionally, MRS repeated regularly during several dozen months in temporal lobe epilepsy patients indicate a marked decrease of NAA/Cr index within the epileptic focus in the temporal lobe.

Some authors indicate altered concentrations of other metabolites in patients with drug-resistant temporal lobe epilepsy. Savic et al. [16], who assessed the levels of glutamine and glutamates (Glx) as well as N-acetylaspartates in 18 patients with MTS, observed a considerable increase of Glx/NAA and Glx/Cr ratios and a decrease of NAA/Cr in the epileptogenetic focus in comparison with the unaffected side.

As it follows from the literature cited above, the methods of optimal assessment allowing detection of pathologies within the medial portions of the temporal lobes are still being sought.

The method of semi-automatic brain-fluin index calculation for the hippocampal region developed by us is a quick and simple method, applicable in everyday practice with the use of a PC.

Conclusions

1. The program for automatic morphometric analysis of hippocampal volume presented in the paper is an easy to use and readily available (it can be used on a PC) tool for quantitative assessment of mesolimbic structures in epilepsy patients.

2. Manual measurement of hippocampal volume allows 100% correct classification of the patients to the control group (CONTR) and the study group (EPI).

3. Thorough analysis of the obtained data allowed to conclude that precise hippocampal volume assessment can

be obtained by combination of both methods, i.e. manual delineation and automatic calculation of brain-fluin index, taking into consideration the total volume of cerebral structures.

4. Ind 3 is a conventional parameter, defined so as to measure the percentage content of hippocampal tissue in relation to the total cranial volume in a way individual for each patient.

Combination of both measurement methods (manual delineation and calculation of brain-fluin index, considering the brain volume index) eliminates the problem of low specificity of the method.

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