We compared the volumes of the superior temporal gyrus, basolateral temporal area, parahippocampal gyrus, hippocampal head, amygdaloid body and the inferior horn of the lateral ventricle in 29 patients with dementia of Alzheimer's type (DAT) and in 14 cognitively normal controls. Measurements were performed on coronal MR images perpendicular to the long axis of the hippocampus then the raw data were normalised for intracranial volume. The volumes of all studied structures were significantly smaller in patients with DAT than in age-matched control group. The differences in the volume between DAT and age-matched control group were the largest for the amygdaloid body and the basolateral temporal area. The discriminant analysis including the volume of both the basolateral area and the left amygdaloid body allows for correct classification of 100% DAT patients and 93% controls. We conclude that the estimation of the volume of the amygdaloid body and basolateral temporal area seems to be the most important factor for DAT diagnosis.

key words: temporal lobe, Alzheimer's disease, magnetic resonance, stereology, discriminant analysis

INTRODUCTION
Dementia of the Alzheimer’s type (DAT) is the most frequent cause (60–90%) of progressive memory impairment in older people [11]. Impairments in episodic memory and medial temporal lobe atrophy are considered to be essential features of Alzheimer’s disease and play an important role in its diagnosis [32, 35].

In patients with progressive memory impairment most of the research is focused on the evaluation of the hippocampus, parahippocampal gyrus and amygdaloid body in spite of the fact that dementia also involves other temporal lobe structures [4, 12, 25, 29, 33–36, 39, 40, 43, 54, 56].

In contrast to CT, magnetic resonance images allow a more accurate delineation of cerebral structures and a more precise estimation of their volume, especially in various pathological conditions [29, 35, 55, 58]. Considerable effort has to be put into determining which structures are of the most importance for the diagnosis of probable Alzheimer’s type dementia. This work tries to answer that question by means of precise, unbiased evaluation of the temporal lobe structures distinguishable during in vivo MR-scanning.

MATERIAL AND METHODS
The sample included consecutively recruited patients with a probable diagnosis of DAT either from the Psychiatric Department of the Medical University of Gdańsk.
Gdańsk or the Regional Psychogeriatric Centre. Patients with dementia related to other reasons (vascular, endocrine, in the course of some encephalopathies or system diseases, hydrocephalus, Pick’s, Huntington’s and Parkinson’s diseases, multiple sclerosis), addicted to drugs or alcohol, or with epileptic, post-traumatic or intracranial haemorrhage were excluded. Finally the 29 patients (11 males and 18 females) aged from 57 to 83 years met the NINCDS-ADRDA [41, 44] and ICD-10 [13] criteria for probable Alzheimer’s disease and the MR images of their brains were used for evaluation of the temporal lobe structures. The stage of the disease was verified by neuropsychiatric examination; the MMSE and GDS scores were produced (Table 1). The dementia of Alzheimer type was accompanied neither by any other neuropsychiatric pathology nor by any vascular changes in the brain, distinguishable during MRI evaluation.

The control group consisted of 14 healthy volunteers (3 males and 11 females) aged from 51 to 84 years without any neurological symptoms of pathological changes in the central nervous system and without any distinguishable signs on MR scans.

**MR imaging**

MRI was performed on 0.5T superconducting MRI scanner (Gyroscan T5, Philips) with the use of standard head coil. In the first step multi-stack scout sequence (FFE M2D, TR/TE/FA 10/2.9/60 Thk/gap 10.0/10.0) and sagittal scout sequence (SE T1, TR/TE 372/15.0, Thk/gap 6.0/1.0) were performed. Axial SE PD/T2 sequence (TR 2200, TE 20/80, Thk/gap 6/0.6 NSA 1 or 2) on the whole brain was used to evaluate the brain structures and to rule out gross pathology as well as to measure the intracranial volume (ICV) — this parameter was used for the data normalisation.

The sagittal scout sequence was used to mark coronal sequence perpendicular to the long axis of the hippocampus (T1W/3D/FFE, TR/TE/FA 30/13/3, Thk/gap 1/0 or 1.5/0, NSA 1).

**Stereology**

Morphometric study was performed on coronal MR images perpendicular to the long axis of the hippocampus by use of semiautomatic method on image analyser Q500MC working under software QWin on Pentium 233 MHz with 17” SVGA monitor. All MRI scans were saved on disk and then the automatic procedure, including sequential reading, contrast enhancing, manual drawing of the structures on the scans, automatic calculation of the cross-sectional area of drawn structures and saving of partial results for consecutive calculation, was used. For the estimation of the volume of the cavum the Cavallieri formula was applied (the estimated volume is a product of the sum of the cross-sectional areas of the structure ($A_i$) and the distance between two consecutive scans ($t = 1$ or 1.5 mm).

$$ \tilde{V} = \sum_{i=1}^{n} V_i \cdot t $$

Along with the volume estimation the coefficient of error (CE) was calculated in worksheet according to the formulas proposed by Geinisman et al. [20]

$$ CE(\tilde{V}) = \frac{\sqrt{\text{Nug}}}{\sum_{i=1}^{n} A_i} + \frac{\text{Var}_{\text{SRS}}}{2} $$

where $\text{Nug}$ (“noise-effect”) was equal to 0 (measurements were done automatically).

$\text{Var}_{\text{SRS}}$ reflects the variability of consecutive cross-sectional areas of the structure on MR scans. The sampling was designed to obtain a CE smaller than 3%.

The following structures were studied within the space bordered by the anterior pole of the amygdaloid body and the posterior pole of the hippocampal head (Fig. 1): superior temporal gyrus (STG), basolateral temporal area (BTG — the region including middle temporal gyrus, inferior temporal gyrus and fusiform gyrus), parahippocampal gyrus (PAH), hippocampus (HIP), amygdaloid body (AA) and the lateral ventricle (LV). Delineations of all studied structures were performed by one rater, highly experienced in neuroanatomy. The first slice taken for the volume estimation was determined by the presence of the distinct amygdala (usually one scan behind the previous image, containing not only the part of the basolateral amygdaloid complex but also the excluded anterior amygdaloid area). Due to differences in the intracranial volume between groups of cases, data for individual variables in each subject were normalised.

**Table 1. GDS and MMSE scores of patients with probable dementia of Alzheimer’s type**

<table>
<thead>
<tr>
<th>MMSE score</th>
<th>Number of patients with GDS score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>21–25</td>
<td>6</td>
</tr>
<tr>
<td>11–20</td>
<td>3</td>
</tr>
<tr>
<td>0–10</td>
<td>0</td>
</tr>
</tbody>
</table>
Outlines of studied structures projected into MRI representative scans through the anterior part of the temporal lobe; AA — amygdaloid nucleus, BTG — basolateral temporal area, HIP — hippocampal head, LV — temporal horn of the lateral ventricle, PAH — parahippocampal gyrus, STG — superior temporal gyrus.

**Figure 1.** Outlines of studied structures projected into MRI representative scans through the anterior part of the temporal lobe; AA — amygdaloid nucleus, BTG — basolateral temporal area, HIP — hippocampal head, LV — temporal horn of the lateral ventricle, PAH — parahippocampal gyrus, STG — superior temporal gyrus.
according to the formula used by Jack et al. [31] and Free et al. [19]:

\[ V_i = \text{est} V_i - B(\text{ICV}_i - \text{meanICV}) \]

where \( \text{ICV}_i \) — intracranial volume of the \( i \)-th case, \( \text{meanICV} \) — mean intracranial volume, \( \text{est} V_i \) — estimated volume of the structure in the \( i \)-th case, \( B \) — coefficient of regression (slope) based on the dependence between the intracranial volume and the volume of the structure.

**Statistics**

For the statistical analysis of the volumetric changes of temporal lobe structures, the ANOVA with repeated measures was used. The goodness of fit with normal distribution was checked by means of the Shapiro-Wilk test, the equality of variances — by means of Bartlett’s test. The diagnosis of SDAT was the main effect for the evaluation. As a repeated measure — the side of the brain (interhemispheric asymmetry) was used. Then the post-hoc honest significant difference test (HSD) was applied to study the differences between groups. The effect of sex was not evaluated. In the case of non-normality and/or the presence of unequal variances, nonparametric analysis was used.

Relations between MMSE scores and the normalised volume of the studied structures were measured by use of Pearson’s correlation coefficients. Effect of age upon the volume of the structures, if significant, was excluded by means of calculation of the partial correlation coefficient.

The stepwise forward discriminant analysis was applied to choose the most important structures for the diagnosis of Alzheimer’s type dementia. The sensitivity and specificity of the “diagnostic test”, consisting of previously chosen best discriminators, were calculated.

All calculations were done in spreadsheet, and statistics were done using two packages (Statistica® v. 5.5, Statsoft, USA, and InStat®, StatGraph, USA). For all tests \( p < 0.05 \) was the level of significance.

All data presented in graphs and tables are normalised.

**RESULTS**

**Main effect, side effects and interactions**

Analysis of variance indicated a significant effect of the diagnosis upon the normalised volume of all studied structures. Their volumes in DAT were smaller than those in the age-matched control group, except for the volume of the temporal horn of the lateral ventricle, for which that parameter reached larger values. Although in the control group significant interhemispheric differences were observed for the normalised volume of the superior temporal gyrus, amygdala and hippocampal head, the latter was the only structure in the DAT group whose volume differed significantly between left and right hemisphere. Thus the significant effect of interaction (\( p < 0.01 \)) between the diagnosis and the occurrence of the process in the specific hemisphere was observed only for the hippocampal head.

**Comparisons between groups**

All studied structures in the left and right temporal lobe were significantly smaller in patients with DAT than in age-matched control group (Table 2, Fig. 2).

In the left hemisphere the differences in the normalised volume between DAT and age-matched control group were the largest for the amygdaloid body, and the basolateral temporal area (36% and 29%, respectively; Fig. 2, 3). A medium degree of the difference of the vol-

<table>
<thead>
<tr>
<th>Structure</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>STG</td>
<td>4.45 ± 0.55</td>
<td>3.84 ± 0.77</td>
</tr>
<tr>
<td>BTG</td>
<td>12.07 ± 1.23</td>
<td>8.61 ± 1.66</td>
</tr>
<tr>
<td>PAH</td>
<td>3.02 ± 0.57</td>
<td>2.24 ± 0.66</td>
</tr>
<tr>
<td>AA</td>
<td>1.27 ± 0.18</td>
<td>0.82 ± 0.24</td>
</tr>
<tr>
<td>HIP</td>
<td>1.41 ± 0.27</td>
<td>1.22 ± 0.25</td>
</tr>
<tr>
<td>LV</td>
<td>0.46 ± 0.36</td>
<td>0.87 ± 0.45</td>
</tr>
</tbody>
</table>

\*significant (\( p < 0.05 \)) interhemispheric difference within control or DAT groups

Table 2. Normalised volume of structures under study shown as mean ± standard deviation. The \( p \)-value concerns the difference between control and DAT group.
The volume of studied structures (mean ± SD) in DAT group in relation to the mean volume of studied structures in control group. For better visualising of data — those concerning the lateral ventricle are not shown.

Figure 2.

Representative scans through the anterior (I), middle (II) and posterior (III) part of the studied area within the temporal lobe in patients with moderate (A) and severe (B) DAT.

Figure 3.
ume between DAT and control group concerned the parahippocampal gyrus (26%). Both the volume of the hippocampal head and superior temporal gyrus were smaller in DAT group only about 14%.

In the right hemisphere, the largest difference in the normalised volume between DAT and age-matched control group was found also for the amygdaloid body and basolateral temporal area (33% and 30%, respectively). The volume of the remaining structures — the parahippocampal gyrus, hippocampal head and superior temporal gyrus were smaller about 23%, 22% and 21%, respectively. The temporal horn of the lateral ventricle was almost two-fold larger in the left as well as right hemisphere.

**MMSE evaluation**

Significant changes of the normalised volume related to MMSE in both hemispheres were found for the basolateral temporal area, amygdaloid body and for the temporal horn of the lateral ventricle (Table 3). Additionally in the left hemisphere the normalised volume of the superior temporal gyrus correlated with MMSE score. Use of the partial correlation coefficient for the elimination of the significant effect of age upon the volume of structures resulted in a significant correlation between the MMSE score and the volume of the left amygdaloid body.

**Discriminant analysis**

At first, stepwise discrimination analysis with all the normalised volumes of studied structures either for the left or for the right hemisphere was applied to choose the best possible set of discriminators on the basis of Wilk’s lambda (the smaller — the larger discriminative power). As a result, the normalised volumes of both the amygdaloid body and basolateral temporal area from right as well as left hemisphere were chosen (the Wilk’s lambda for each variable was below 0.6 and differed significantly from other coefficients). The chosen set of four independent variables gave the R-squared coefficients for each variable below 0.3, indicating that only a small part of its variance could be predicted from the other variables, which meant that multlinearity was not a problem. Finally, from the set of four variables, three were chosen — the normalised volume of the left amygdaloid body, left basolateral temporal area and right basolateral temporal area (Wilk’s lambda 0.34, p < 0.001; Fig. 4). If the volume of chosen structures in the diagnostic test were included, a sensitivity of 100% and specificity of 92.9% could be achieved.

**DISCUSSION**

In patients with progressive memory impairment, most of the research is focused on the evaluation of the hippocampus, parahippocampal gyrus and amygdaloid body [4, 12, 25, 29, 33–36, 39, 40, 43, 54, 56]. As the process of dementia also involves other structures of the temporal lobe, we made an effort to estimate the volume of the superior temporal gyrus and basolateral temporal area (BTG — the region including middle temporal gyrus, inferior temporal gyrus and fusiform gyrus).

Magnetic resonance, due to good tissue characterisation and white-grey matter differentiation in the comparison with computer tomography, allows for a more accurate delineation of cerebral structures, especially

<table>
<thead>
<tr>
<th>Structure</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
</tr>
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<tbody>
<tr>
<td>STG</td>
<td>0.37; p &lt; 0.05</td>
<td>0.31; NS</td>
</tr>
<tr>
<td>BTG</td>
<td>0.62; p &lt; 0.001</td>
<td>0.47; p &lt; 0.01</td>
</tr>
<tr>
<td>PAH</td>
<td>0.36; NS</td>
<td>0.34; NS</td>
</tr>
<tr>
<td>AA</td>
<td>0.57; p &lt; 0.01</td>
<td>0.55; p &lt; 0.01</td>
</tr>
<tr>
<td>partial r (MMSE</td>
<td>AGE) 0.45; p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>HIP</td>
<td>0.21; NS</td>
<td>0.30; NS</td>
</tr>
<tr>
<td>LV</td>
<td>−0.49; p &lt; 0.01</td>
<td>−0.46; p &lt; 0.05</td>
</tr>
</tbody>
</table>

**Figure 4.** The contour plot of the relation between the volume of left and right basolateral temporal area and the volume of the left amygdaloid body. Lines represent the distance-weighted least squares fitted curves related to the mean and standard deviation of the volume of the left amygdaloid body both in control and DAT groups.
in a pathological atrophied brain [29, 35, 55, 58]. To obtain maximum accurate results, the MRI scans were performed in 1 or 1.5 mm slice thickness (3D volumetric method), comparably to the methods of other authors [19, 27, 45, 52] — several scans were used for the volume estimation, resulting in the decrease of the coefficient of error of the volume estimation to values smaller than 3%, this value is even smaller than the level of statistical significance.

Due to the difference in the intracranial volume between groups — to compare the volume of structures — normalisation should be implemented [19, 31, 53]. For normalisation different authors use various methods — as a reference point the total brain volume, the total or partial intracranial volume, or even the cerebral surface on the selected scans was used [3, 10, 12, 19, 25, 27, 29–31, 38–40, 46]. In our study we implemented the method of volume normalisation used by Jack et al. [31]. According to their observations [31] the covariance approach gives better distributional properties than ratio adjustment.

Generally most authors found the presence of interhemispheric asymmetry in the volume of temporal lobe structures. However, differences between papers concern the direction of the asymmetry as well as the question of whether they persist in brains of patients with DAT. Our results regarding control group correspond to those in other papers as far as the amygdaloid body [36, 52], hippocampal head [3, 9, 21, 28, 31, 52, 55], and superior temporal gyrus [21] are concerned. Other authors found this difference as non-significant or directed in the opposite side [2, 3, 25, 33, 39, 55]. Results concerning the asymmetry of the temporal lobe structures in DAT varied considerably between the papers [33, 36, 40] — and, what can be assumed, are connected predominantly with the variability of the severity of the degeneration process in studied cases. Among the other reasons there are factors important for estimation of the volume — delineations of structures’ borders and error of the volume estimation. Some authors tried to find even the relation between the stage of the disease and the presence of asymmetry [57]. We have not found such a relation in our material. Only the volume of the hippocampal head was different between the left and right side, additional- ly there was no significant effect of the stage of the disease upon the interhemispheric differences of the volume of all studied structures.

Atrophy of the temporal lobe structures (mainly the hippocampus, amygdaloid body and parahippocampal gyrus), as well as general atrophy of the grey and white matter, basal ganglia and corpus callosum, were reported in many neuropathological and radiological papers [8, 14, 24, 29, 33, 42, 46, 49, 51, 59].

In our material the volumes of all the studied structures were smaller in DAT than in age-matched control group, except for the volume of the temporal horn of the lateral ventricle, which was larger in DAT. The degree of atrophy varied considerably among the DAT group. The coefficients of variability of the atrophy in DAT group in relation to the mean value for the control group extended from 19% to 33% (excluding the temporal horn of the lateral ventricle). For all studied structures an overlap was found between results for patients with DAT and controls; it corresponds to results of some authors [29, 39], while Kesslak et al. [33] reported no overlap for the volumes of the hippocampus or parahippocampal gyrus. According to Jack et al. [29, 30] the volume of the hippocampal formation separated in the best way (but not completely) DAT patients from the controls.

A statistically significant volume loss of the hippocampus and amygdaloid body in DAT compared to age-matched control group has often been observed in neuroradiological examinations, as well as in post-mortem studies [5, 12, 25, 29, 30, 33, 34, 38, 39, 45]. In our results from the group of DAT, the atrophy of the amygdaloid body of the left (36%) and right (33%) hemisphere was one of the largest among studied structures, while the atrophy of the hippocampal head was smaller and reached only about 14% in the left and 22% in the right hemisphere.

Mori et al. [45], among structures undergoing atrophy, included also the amygdaloid body; however, according to other authors the atrophy of this structure was not significant [37]. The decrease of the volume of the amygdaloid body ranged from 26% to 55%, being statistically significant, however Killiany et al. [34] did not find a significant difference between DAT patients and age-matched control group. Decrease of the volume of the hippocampus in Alzheimer’s disease was from about 20% to 40% [7, 12, 16, 23, 37, 50, 51, 59], but some authors reported much lower values [14, 36, 52].

Ikeda et al. [25] reported that also the parahippocampal gyrus was significantly smaller in patients with possible and probable Alzheimer’s disease than in controls. This corresponded to our results and observations of other authors [26, 48]. Significant atrophy of the parahippocampal gyrus was seen even in the early stages of Alzheimer’s disease [25, 33, 45, 47]. These observations correspond and are related to the significant decrease of the total number of neurons in the entorhinal cortex — the main component of the parahippocampal gyrus [5, 6].
In contrast to the vast amount of data concerning the atrophy of the amygdaloid body, hippocampal formation and parahippocampal gyrus, observations concerning other structures of the temporal lobe are scanty [1, 48], in spite of their role in memory processes. In our study the atrophy of the basolateral area (the region including inferior temporal, middle temporal and fusiform gyrus) and of the superior temporal gyrus was significant in both hemispheres; additionally the atrophy of the former reached the values close to those for the amygdaloid body.

Results of numerous studies suggested that the atrophy of the temporal lobe structures was correlated with the severity of Alzheimer’s disease [26, 33, 45, 46, 49]. We have found the correlation between the MMSE scores and the volume of the basolateral area, amygdaloid body and inferior horn of the lateral ventricle in both hemispheres. Moreover, in DAT group both MMSE score and the volume of the left amygdaloid body correlated significantly with age. Due to these circumstances, to eliminate the effect of age upon the volume of the amygdaloid body, partial correlation coefficient was calculated, resulting in the decrease of the coefficient of correlation from 0.57 to 0.45. The final effect of MMSE score following the exclusion of influence of age was significant, too. Some authors did not find a correlation between the volume of the amygdaloid body and MMSE score in patients with DAT [12, 36, 39]. Moreover, in our study (like in the study by Mori et al. [45]), the atrophy of the hippocampal head did not correlate with MMSE score; other authors observed the correlation between the severity of the cognitive impairment and the atrophy of the hippocampus and/or parahippocampal gyrus [33, 36, 39].

Due to the increasing role of MRI in the diagnosis of possible DAT, the authors have made a tremendous effort to find the structure (or structures) of the temporal lobe able to discriminate patients with probable Alzheimer’s disease from control cases. The ability to repeatably distinguish the structures’ borders on MRI scans was of great importance for such a procedure [45]. First observations have indicated the discriminative value of the volume either of the hippocampal formation or amygdaloid body. Laakso et al. [38] found the hippocampus to be the structure of the most discriminative value, although not exclusively for the diagnosis of Alzheimer’s disease; similarly Jack et al. suggested that the hippocampal volume should have been enough for discrimination between groups [29, 30]. This was also confirmed and described in detail by Wolf et al. [57]; they found differences in discriminative power for hippocampal subdivisions. According to them the hippocampal body (not head) has the best discriminative value. Lehericy et al. [39] reported that volume measurements of the amygdaloid body led to correct diagnosis in 94% of patients with Alzheimer’s disease. Due to the differences between cases, our results, indicating smaller discriminative power of the volume of the amygdaloid body, are not comparable. In another paper [36] they defined more precisely that the diagnostic test based on the estimation of the volume of left amygdaloid body allows for the correct diagnosis of DAT in about 76% of cases from DAT group and in about 72% — from the control group. Other data suggested the value of the multivariable diagnostic approach, allowing for the distinguishing of from 50% to 85% cases with Alzheimer’s disease [16, 18, 22, 38]. In our material the improvement of the specificity could be achieved by adding the volume of the right amygdaloid body to the diagnostic test based only on the volume of the left amygdaloid body. Results of our stepwise discriminative analysis suggest that only a combination of the volumes of a few structures allows for better differentiation of DAT patients from the control group. This has corresponded to the results of other authors [15, 34, 37, 39, 48]. According to Pearlson et al. [48], the left amygdala and entorhinal cortex were the best discriminators for Alzheimer’s disease but their estimations were done only on eight control cases and nine with Alzheimer’s disease. Laakso et al. [37] included the volume of the left frontal lobe among the set of discriminators consisting of the left and right hippocampus and found that adding the volume of the amygdala did not improve statistics, but the stage of the disease as measured by MMSE score was considerably different from that in our studies (22.8 versus 14.8, respectively). Moreover Kiliarly et al. [34] found that the hippocampus and temporal horn of the lateral ventricle seemed to be markers for mildly impaired patients and they observed no discriminative value of the amygdala as well as basal forebrain, but again their results were based on the estimation of a small group of patients with considerably higher MMSE scores. Characteristically in the studies of Lehericy et al. [39], where AD group consisted of patients with MMSE scores closer to those found in our results, the set of best discriminators included the amygdaloid area but also the hippocampal formation. The diagnostic value of the temporal neocortex was noticed by Erkinjutti et al. [17]; for this structure they achieved the specificity and sensitivity of more than 80%, but their studies did not include the amygdaloid body. Our studies, involving the volume of temporal basolateral isocortex besides the volume of the amygdala, allowed for the correct classification of more than 97% of examined cases from DAT group and in about 72% — from the control group. Other data suggested the value of the multivariable diagnostic approach, allowing for the distinguishing of from 50% to 85% cases with Alzheimer’s disease [16, 18, 22, 38]. In our material the improvement of the specificity could be achieved by adding the volume of the right amygdaloid body to the diagnostic test based only on the volume of the left amygdaloid body. 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subjects (100% DAT patients and 93% controls). Moreover the only not-properly discriminated subject was 86 years old. In spite of the statistical significance of the discriminative power of chosen structures (the basolateral temporal area and amygdaloid body), the results indicating their ability to be included in the diagnostic test for probable Alzheimer’s disease should be repeated on larger material.

ACKNOWLEDGEMENTS

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