Study of Cerebrospinal Fluid Tissue Transglutaminase, T-TAU, Amyloid B_{42} in Alzheimer's Disease

Azza A Ghali¹, Manal El Batch¹, Wafaa Ibrahim², Gihan Farouk³
Departments of Neuropsychiatry¹, Medical Biochemistry², Clinical Pathology³, Tanta University

ABSTRACT

Biochemical markers for Alzheimer disease would be of great value, especially to help in early diagnosis of the disease. The current study has focused on three candidates that have been suggested to be indulged in the pathogenesis of Alzheimer’s disease (AD): Tissue transglutaminase (tTG) activity, β-amyloid42 (Aβ 42) and total T-tau (T-tau). The study included 15 patients with probable AD, 15 patients with probable vascular dementia (VaD) in addition to 10 control subjects without neuropsychiatric diseases. The results of this study revealed that the CSF levels of total T-tau and activity of tTG, were significantly higher in patients with AD when compared with VaD and control. Also, CSF Aβ_{42} of patients with Alzheimer’s disease were significantly low when compared with vascular dementia, and controls. The sensitivity and specificity of CSF T-tau and Aβ_{42} were found to be high for differentiation of AD patients from controls, but their specificity against (VaD) is moderate. So, measurement of CSF tTG, T-tau and Aβ_{42} level in AD patients may provide useful and relatively simple biochemical tests for differentiating Alzheimer’s Disease from vascular dementia. In addition, the diagnostic usefulness of the CSF content of both T-tau and Aβ_{42} is superior to either measure alone with high sensitivity and specificity for prediction of AD, and can be recommended as an aid to evaluate individuals suspected of having dementia. (Egypt J. Neurol. Psychiat. Neurosurg., 2006, 43(2): 321-330)

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia that affects men and women equally, and characterized by progressive deterioration of cognitive functions such as memory, and language and visuospatial orientation. Associated symptoms are mood and behavioral changes. The prognosis is poor with no cure is available¹².

Underlying neuropathological changes in AD are the accumulation of senile plaques (SPs) and neurofibrillary tangles (NFTs). SPs are made up mainly of β-amyloid, especially the 42-amino-acid isoform, β-amyloid42 (Aβ_{42}). The major constituent of NFTs is a cytoskeleton-associated protein called T-tau, which is hyperphosphorylated in NFTs³. During the progression of AD a substantial amount of neurons degenerate in the brain. The mechanisms of cell death involved in AD have not been fully elucidated.

Amyloid β(Aβ) is the major constituent of the characteristic SPs and cerebrovascular amyloid found in the brains of AD patients. Aβ_{42} is proteolytically derived from Aβ_{40} precursor protein (APP). APP may normally be involved in cell adhesion related to synaptic maintenance. Loss of synapses correlates with dementia, suggesting that synaptic deficits may underlie AD³. The major products of this proteolytic cleavage process contain either 40 or 42 residues (Aβ_{40} or Aβ_{42}). Aβ_{42} is continuously produced in a soluble form and is found in CSF suggesting that its production and secretion are part of a physiological process⁵. Overproduction of Aβ_{40,42} or failure to clear this peptide leads to AD, through amyloid deposition associated with cell death⁶.

The microtubule-associated protein, T-tau, is a normal human brain phosphoprotein, which
binds to microtubules in the neuronal axons, thereby promoting microtubule assembly and stability. Both normal and hyperphosphorylated T-tau are dispersed to the CSF. T-tau is an in vitro tTG substrate, being cross-linked and/or polyaminated, the cross linked filamentous aggregates of T-tau were insoluble, suggesting that this may be a contributing step in the process leading to the formation of NFTs. The Glutamine and Lysine residues in T-tau that are modified by tTG in vitro are located primarily within or adjacent to the microtubule-binding domains. If tTG is involved in T-tau aggregation and NFTs, it can be hypothesized that tTG activity and/or expression may be elevated in AD.

Tissue transglutaminase (tTG) (EC 2.3.2.13) is a multifunctional protein that is likely to play a role in numerous processes in the nervous system. tTG post-translationally modifies proteins by trans-amidation of specific polypeptide bound glutamines. This action results in the formation of protein cross links or the incorporation of polyamines into substrate proteins, modifications that likely have significant effects on neural function. At first the proteasome machinery can recognize and degrade the cross-linked proteins, but over time the proteasome machinery may be overwhelmed and protein aggregates will accumulate. It was suggested that the protein polymers resulting from tTG-catalyzed reactions may play a role in commitment of cells to undergo apoptosis. The most ubiquitously expressed member of the TGase family, known as tissue TGase (tTG) or TG2, which catalyzes the production of epsilon-lysine to gamma-glutaminyl isodipeptide bonds. It differs from other members of the TGase gene family in this regard and may implicate it in ‘switches’ from life or trophic signaling to those associated with apoptosis. In this regard, recent data indicate that one or more TGases are involved in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. As do many genes, particularly those highly expressed in the CNS, tTG undergoes alternative processing. Elevated expression and alternative splicing, resulting in a short (S) isoform of tTG with more active cross-linking activity, are associated with increased neuronal loss in affected regions in the demented brain. An increase in tTG protein level is found in postmortem AD brains as well as in Huntington's disease. Many polypeptides associated with neurodegenerative diseases are suggested to be putative transglutaminase substrates such as beta amyloid protein of Alzheimer's disease, microtubule-associated proteins and neurofilaments.

An analysis of symptoms and signs, blood studies and brain imaging are major ingredients of the clinical diagnostic work-up. However, the diagnosis based on these instruments is unsatisfactory, indicating the need of highly sensitive and reliable approaches, selective for AD and based on biological markers. Therefore genetic and/or biochemical markers that support the clinical diagnosis and can distinguish AD from cognitive symptoms attributable to ageing and from other dementias will be of great value. The identification of such accurate markers for the early diagnosis of AD is mandatory for the development of efficient pharmacological treatment, since therapy should be initiated at an early stage of the disease, before extensive and irreversible brain damage has occurred. As the intercellular space in the brain is in direct contact with the CSF, biochemical changes in the brain may be reflected by CSF analyses that should reflect the patho-physiological mechanisms of AD. So, the aim of the current study is to assess CSF changes in tissue transglutaminase activity, T-tau and Aβ42 in AD and VaD patients. Also, to determine the sensitivity and specificity of T-tau and Aβ42 combination as predictors of AD and its severity.

**SUBJECTS AND METHODS**

This study included 3 groups of matched age: AD group comprised of 15 patients with the clinical diagnosis of “probable AD”, 15 patients with the clinical diagnosis of “probable” vascular dementia (VaD), and The healthy control group consisted of 10 subjects. Control subjects were
undergoing spinal anesthesia for orthopedic surgery, without histories, symptoms, or signs of psychiatric or neurological disease, malignant disease, or systemic disorders (for example, rheumatoid arthritis, infectious disease). No subject had cognitive symptoms.

All subjects underwent a comprehensive clinical evaluation including medical history, physical, neurological, and psychiatric examinations. The presence or absence of dementia was diagnosed according to the Diagnostic and Statistical Manual of mental Disorders, fourth edition (DSM IV) criteria. Probable AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer disease and Related Disorders (NINCDS-ARDA) criteria. The miniminal state examination (MMSE) was used to judge the severity of the dementia. Probable Vascular Dementia was diagnosed by the Hachinski Ischemic Scale (HIS), and according to National Institute of Neurological Diseases and Stroke-Association International pour La Rechache et l Enseigment en Neuroscience (NINDS-AIREN) criteria. Mixture forms (AD plus) were interpreted as AD according to Bonelli et al.

Patients with probable AD had insidious onset and even progressive dementia which could not explained by systemic or brain disorders other than A.D. No patients had prominent frontal lobe symptoms or history, clinical, or brain imaging signs of cerebrovascular diseases. Patients with probable AD were classified into mild AD (MMSE score > 14) and severe AD (MMSE score < 14). Probable vascular dementia was diagnosed in patients with history of transitory ischemic attacks or stroke episodes with temporal relation to the development of dementia; together with CT and/or MRI findings of lacunes, infarcts, or white matter lesions. Other forms of dementia (e.g., Huntington, disease, progressive supranuclear palsy) were excluded in this study.

Routine laboratory tests, EEG, and brain MRI were done. All subjects underwent lumbar puncture for diagnostic reasons after they gave informed consent and undergo CSF analyses. After centrifugation to eliminate cells and other insoluble material, all CSF samples were frozen at -70°C pending biochemical analyses. 1) CSF-T-tau was determined using a sandwich ELISA (BioSource, International, Inc.), constructed to measure total T-tau (both normal T-tau and phosphorylated -T-tau), as described previously in accordance with the manufacturer’s instructions25, 2) CSF Aβ42 was determined using a sandwich ELISA (Immuno Biological Laboratories) as described by Mehta et al.26. 3)CSF tTG activity was determined according to De Macedo et al.27, and CSF protein was determined according to modified Lowry et al.28 using bovine albumin as a stander. The enzyme activity was expressed as anilide umol/min/mg protein.

Statistical analysis: results were expressed as the mean±SD. Mean of different groups was compared using a one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls test. P<0.05 was accepted as significant. Correlation between variables was evaluated using Pearson’s correlation coefficient. Cut-off point of T-tau and Aβ42 was determined according to Andreasen et al.29,30.

**RESULTS**

Analyses of the results:

Table (1) shows the clinical characteristics of studied groups in which neither the age nor the duration of dementia significantly differ between AD, VaD and control, but, the mean MMSE score showed significant difference between the studied groups. The mean values of CSF biomarkers in each group studied have been shown (Table 2). The highest significant values of CSF T-tau and tTG activity were observed in the two AD subgroups as compared with both control and VaD, while the lowest significant values of Aβ42 were found in severe AD as compared with both control and VaD. No significant correlation was found in the AD group, between CSF changes in tTG activity, T-tau protein, Aβ42, and either age, severity or duration of the disease (Table 2). An
An inverse correlation was found between CSF concentrations of T-tau and Aβ42 within the AD group. No significant correlation was found between tTG activity and both T-tau and Aβ42. Using a cut-off point of T-tau = 306 (pg/ml) and Aβ42 = 500 (pg/ml), the sensitivity and specificity of CSF-T-tau and Aβ42 was calculated as diagnostic markers for AD. The sensitivity was defined as the ability of CSF-T-tau and Aβ42 to identify AD. The specificity was defined as the ability of CSF-T-tau and Aβ42 to exclude AD, whereas the positive predictive value was defined as the proportion of correctly diagnosed patients with AD of all patients with high CSF-T-tau and low Aβ42 (Altman et al., 1983). 9/10 (90%) of the controls had normal levels of both CSF-T-tau and CSF-Aβ42, while one control (10%) had abnormal values. In contrast, AD patients both mild and severe, 14/15 (93.33%) had high CSF-T-tau and low CSF-Aβ42, while 1/15 (6.66%) had normal levels of both markers. As regards probable VaD 9/15 (60%) had high CSF-T-tau and low CSF-Aβ42, while 6/15 (40%) had normal levels of both markers (Table 4). Thus, the sensitivity for high CSF-T-tau and/or low CSF-Aβ42, for the prediction of AD was (93.33%), while the specificity was (90%) when compared with the control and 40% when compared with VaD.

### Table 1. Clinical characteristics of the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=10)</th>
<th>Alzheimer’s disease (n=15)</th>
<th>probable vascular dementia (n=15)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>67±4</td>
<td>65±7</td>
<td>71±4</td>
<td>66±8</td>
<td>1.45</td>
</tr>
<tr>
<td>Sex (♂/♀)</td>
<td>5/5</td>
<td>2/4</td>
<td>4/5</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Duration of dementia (months)</td>
<td>-</td>
<td>38 ±27</td>
<td>40±28</td>
<td>38±21</td>
<td>0.48</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3±5</td>
<td>22.6 ±4.5</td>
<td>10±1.8</td>
<td>15±5.8</td>
<td>30.63</td>
</tr>
</tbody>
</table>

All groups are significantly differ.

### Table 2. CSF levels of T-tau, Aβ42, tTG activity among the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=10)</th>
<th>Alzheimer’s disease (n=15)</th>
<th>probable vascular dementia (n=15)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-tau (pg/ml)</td>
<td>225±88</td>
<td>300±90</td>
<td>700±270</td>
<td>280±130</td>
<td>17.29</td>
</tr>
<tr>
<td>All groups are significantly differ except mild vs. control, VaD vs. control and mild vs. VaD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ42 (pg/ml)</td>
<td>875±262</td>
<td>400±100</td>
<td>255±87</td>
<td>550±206</td>
<td>17.08</td>
</tr>
<tr>
<td>All groups are significantly differ except mild vs. severe and mild vs. VaD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tTG activity (anilide µmol/min/mg protein)</td>
<td>0.41±0.03</td>
<td>0.75±0.09</td>
<td>0.89±0.07</td>
<td>0.51±0.09</td>
<td>81.87</td>
</tr>
<tr>
<td>All groups are significantly differ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

324
Table 3. Correlation between T-tau, Aβ_{42}, tTG activity and other variables in Alzheimer's disease groups (n=15).

<table>
<thead>
<tr>
<th>Variables</th>
<th>T-T-tau</th>
<th>A β_{42}</th>
<th>tTG activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.20</td>
<td>-0.18</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of dementia (month)</td>
<td>0.23</td>
<td>0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.28</td>
<td>0.22</td>
<td>0.07</td>
</tr>
<tr>
<td>T-T-tau (pg/ml)</td>
<td>-</td>
<td>-0.39*</td>
<td>-0.32</td>
</tr>
<tr>
<td>A β_{42} (pg/ml)</td>
<td>-0.39*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tTG activity (anilide μmol/min/mg protein)</td>
<td>0.33</td>
<td>-0.32</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. Sensitivity and specificity of the combined CSF T-tau and Aβ_{42} in Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut-off Value</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Accuracy</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Alzheimer’s disease (n=15)</td>
<td>T-tau=306 (pg/ml) Aβ_{42}=500(pg/ml)</td>
<td>93.33%</td>
<td>90% (AD vs. C) 90% (AD vs. VaD)</td>
<td>92%</td>
<td>93.33%</td>
</tr>
</tbody>
</table>

Aβ_{42} = amyloid beta, AD= Alzheimer’s disease, VaD= vascular dementia, C = healthy control, PPV= positive predictive value

**DISCUSSION**

The antemortem diagnosis of AD requires time-consuming and costly procedures. Also, the accuracy of the clinical diagnosis at the general hospitals is probably even lower, especially in the early stages of the disease when the symptoms are indistinct. Therefore, biochemical tests that can direct the physician rapidly to the correct diagnosis should be able to detect a fundamental feature of neuropathology. Furthermore, its sensitivity for detection of AD as well as its specificity for discrimination of AD from other dementia disorders should exceed 80%. A marker for AD should also be reliable, reproducible, noninvasive, simple to perform in clinical routine and inexpensive. Measurement of single biochemical markers in cerebrospinal fluid (CSF) shows robust alterations that highly correlate with the clinical diagnosis of AD but generally lack sufficient diagnostic accuracy. So, in the present study combined CSF measurements of T-tau (as a marker for neuronal degeneration), Aβ_{42} (as a marker for amyloid beta metabolism, and possibly for the formation of senile plaques) and tTG (as a marker for apoptosis) in 30 patients who underwent diagnostic workup for dementia and in 10 healthy control subjects was done.

In the current study, there was a significant increase in CSF activity of tTG in dementia groups as compared with the control, with a significant change on comparing probable AD with probable VaD. This findings came in accordance with the results Lesort et al., who found that tTG level and activity are elevated in both Alzheimer's and Huntington's disease in post mortem. Johnson and coworkers found that the levels of tTG, as determined by quantitative immunoblotting, were elevated approximately 3-folds in Alzheimer disease prefrontal cortex, compared to control and there were not significant differences in tTG levels in the cerebellum between control and Alzheimer disease cases. This elevated level of tTG may be related to neurofibrillary pathology which is usually abundant in the prefrontal cortex and not in the cerebellum which is usually spared in Alzheimer...
disease. They suggested that tTG could be a contributing factor in neurofibrillary tangle formation because tTG is calcium-activated, and tau is an excellent substrate of this enzyme in vitro. The increased intracellular calcium levels in AD activate tTG which converts tau to neurofibrillary tangles\textsuperscript{32,33}. Furthermore, Bonelli et al.\textsuperscript{16} proposed that the concentration of CSF tTG in relation CSF tau and \( \text{A}\beta \) is an indicator for acute cell death in vivo. The CSF tTG levels appears to be elevated in AD patients due to the increased apoptotic process; the protein seems to be released into the extracellular space after cell disruption. Therefore, inhibition of transglutaminase-induced cross-linking may provide a novel strategy for treatment of AD. The high CSF activity of tTG and MMSE shows that tTG may not serve as an indicator for mental decline.

It has been suggested that CSF T-tau concentrations are a good reflection of the actual degree of neurofibrillary degeneration in the brain, and implying that CSF T-tau concentrations may increase with increasing neurofibrillary tangles (NFTs) load and thus with disease progression\textsuperscript{34}. The data presented here in confirmed previous findings of Andreassen et al.\textsuperscript{35}; Galasko et al.\textsuperscript{36}, and Rösler et al.\textsuperscript{37}, of a pronounced increase in CSF-T-tau in Alzheimer’s disease and suggested that the CSF T-tau levels reflect the degree of neuronal (especially axonal) degeneration and damage \textsuperscript{38}, as evidenced by a transient increase in CSF T-tau after acute stroke\textsuperscript{39}. This increase probably reflects leakage of T-tau from damaged neurons to the CSF\textsuperscript{30}. An increased level of CSF T-tau is indeed not a specific marker for AD, but appears also in other neurological diseases, such acute cerebral stroke, Creutzfeldt-Jakob disease, frontotemporal dementia, dementia with Lewy’s bodies or Parkinson’s disease. However, CSF T-tau is generally lower in these pathologies than in AD\textsuperscript{30}. Also, Mulder et al.\textsuperscript{40}, and Parnetti et al.\textsuperscript{41} found increase of CSF T-tau in AD in the earlier stages of dementia, which makes this measurement useful for early diagnosis of AD. In the present study there was no correlation between CSF-T-tau and duration of dementia which came in accordance with Iose et al.\textsuperscript{41}. These findings suggested that high CSF-T-tau concentrations are present during the whole course of the disease. It is possible that the same high CSF-T-tau concentrations are also found before the onset of clinical dementia. If so, CSF-T-tau may be useful for selection of patients with early memory disturbances for clinical drug trials\textsuperscript{20}.

Concomitantly it has been found that CSF-T-tau has a high sensitivity for the diagnosis of AD\textsuperscript{29}. In total, 41/43 (95%) patients with AD had a CSF-T-tau concentration above the cut off level of 306 pg/ml in healthy controls. However, the specificity was lower, as almost all (86%) patients with VaD also had high CSF-T-tau concentrations. In the current study, high CSF-T-tau concentrations were also found in patients with VaD, resulting in a low diagnostic specificity of CSF-T-tau for AD. The high CSF-T-tau concentrations found in VaD may in part be explained by the fact that, these patients may, in addition to cerebro-vascular pathology, have concomitant AD pathology, which is impossible to be excluded clinically. Indeed, several neuropathological studies found that a high proportion (40–80%) of clinically diagnosed patients with VaD have notable concomitant AD pathology\textsuperscript{32,43}.

The central protein in SPs is \( \text{A}\beta_{42} \). It is produced and secreted from human cells as a result of normal cellular processing of the larger transmembrane protein APP\textsuperscript{44}. It is possible that \( \text{A}\beta_{42} \) accumulation triggers the hyperphosphorylation of T-tau protein which precedes the assembly of these molecules into filaments\textsuperscript{5}. Previous studies came in accordance with the results of the current study that demonstrated a moderate to marked decrease in CSF \( \text{A}\beta_{42} \) in AD with no significant correlation with age, MMSE or duration of AD symptoms\textsuperscript{29,45}. The possible cause of low CSF- \( \text{A}\beta_{42} \) levels, may be, axonal degeneration and entrapment in narrow interstitial and subarachnoid drainage pathways\textsuperscript{26,47}. The lack of a clear relationship among CSF \( \text{A}\beta_{42} \), level, severity of dementia, and duration of disease in this study is consistent with studies showing that plaque accumulation and brain amyloid burden do not correspond to duration and
severity of AD. In contrast, Csernansky et al. found that increased severity of dementia was correlated with increased CSF T-tau concentrations and decreased Aβ42 concentrations. The mean sensitivity of CSF Aβ42 for discrimination between AD and normal aging is approximately 86%, while the specificity is approximately 91%. On the other hand, the specificity for discrimination of AD from other disorders is moderate. Low levels of Aβ42 in CSF have been found in other neurodegenerative disorders. Therefore, in the present study concomitant measurements of CSF T-tau and Aβ42 was performed which have been suggested to increase the diagnostic precision of AD. These biochemical markers seem to have clinical value in the very early phase of probable AD and patients with low CSF Aβ and high CSF T-tau have a strong likelihood of having AD. Conversely, patients who exhibit low T-tau and elevated Aβ42 are free of AD. Andreasen and his colleagues found that, the sensitivity for the diagnosis of mild cognitive impairment by using the combination of T-tau and Aβ42 was 75%. These results confirm the findings of aberrant CSF T-tau and Aβ42 concentrations early in the course of the disease, independent of disease progression. Also, it has been deduced that the CSF markers (T-tau and Aβ42) should be combined with the clinical information and brain-imaging techniques. Finally, the current study concluded that, the sensitivity and specificity increased if CSF-T-tau and CSF- Aβ42 were used together. The level of CSF-T-tau has been suggested to reflect the neuronal and axonal degeneration in AD and/or the formation of neurofibrillary tangles, while the level of CSF- Aβ42 has been suggested to reflect the deposition of β-amyloid in senile plaques, with lower levels excreted to the CSF. Thus, both these analyses probably reflect central pathogenic processes in the AD brain, which, however, may vary in intensity between patients. Therefore, it seems logical that the combined use of these markers will increase the sensitivity, specificity and adds to the accuracy of an AD diagnosis.

Conclusion: the present results suggested that tTG may be a powerful biochemical marker of the degenerating process in vivo. It may serve as completion of CSF analysis in the diagnosis of dementing disorders and may be a simple way of assessing the efficacy of possible new antiapoptotic drugs. In addition, the diagnostic usefulness of the CSF content of both T-tau and Aβ42 is superior to either measure alone with high sensitivity and specificity for prediction of AD, and can be recommended as an aid to evaluating individuals suspected of having dementia.

REFERENCES

دارسة نشاط إنزيم الترانس جلوتاميناز النسيجي وبروتين التاو و البيتا اميلويد في السائل المخى الشوكي في مرض عته الزهايمر

لا يزال تشخيص مرض عته الزهايمر يعتمد بالأساس على استبعاد الأمراض الأخرى التي قد تشتبه فيها من حيث العلامات الإكلينيكية وهذا التشخيص يفيد إلى الحساسية والخاصة لهذا المرض ولهذا اتهمت الأبحاث في الفترة الأخيرة لعثور أي من المؤشرات الكيميائية والتي تتميز بحساسية عالية لتشخيص مرض عته الزهايمر. وقد صمم هذا البحث لدراسة التغييرات في مستوى نشاط إنزيم الترانس جلوتاميناز النسيجي وبروتين التاو والبيتا اميلويد في سائل الدماغ الشوكي في مرضي الزهايمر وكذلك اختبار مدى حساسية وخصائية بروتين التاو والبيتا اميلويد في تشخيص المرض، وقد شملت الدراسة 15 مريضاً من المختبر إصابتهم بمرض عته الزهايمر و 15 مريضاً من المختبر إصابتهم بمرض الاعتي الناتج عن قصور في الدورة الدموية المخية بالإضافة إلى 15 شخص سليم استخدموا كعينة ضابطة. وقد وجد من خلال هذا البحث أن هناك زيادة في نشاط إنزيم الترانس جلوتاميناز النسيجي بالإضافة إلى نقص في مستوى بروتين البيتا اميلويد وزيادة في بروتين التاو في مرضى عته الزهايمر. وهذه التغييرات كانت ناتجة عن الفحص في الفئران المخية المخية. وقد قادت هذه الدراسة إلى استنتاج أن هذه المؤشرات الثلاثة من الممكن استخدامها في التشخيص المبكر لمرض عته الزهايمر.