Low prevalence of amyloid and tau pathology in drug-resistant temporal lobe epilepsy

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Abstract

Objective: Cognitive impairment is common in patients with chronic drug-resistant temporal lobe epilepsy (TLE). Hyperphosphorylated tau (pTau) and amyloid-β (Aβ) plaques, pathological hallmarks of Alzheimer disease, have been hypothesized to play a mechanistic role. We investigated Aβ plaques and pTau prevalence in TLE patients who underwent resective surgery and correlated their presence with pre-operative psychometric test scores and clinical factors.

Methods: Patients were retrospectively selected from the epilepsy surgery register of the Royal Melbourne Hospital, Australia. Sections from the resected temporal lobe were immunostained for pTau and Aβ plaques (antibodies: AT8, 1E8). The presence and severity of pathology were correlated with clinical characteristics, verbal and visual learning functions as measured by the Verbal Pair Associates Test (VPA) and Rey Complex Figure Test.

Results: 56 patients (55% female) aged 20 to 68 years (median 34 years) at surgery were included. Aβ plaques were detected in 4 patients (7%), all at the moderate level. There was no difference in duration, age of onset of epilepsy, or side of resection between patients with and without Aβ plaques. Sparse pTau were found in 2 patients (3.5%). Both had moderate Aβ plaques and were over 50 years of age. Patients with Aβ plaques had a lower median score for the VPA hard assessment compared to those without (0 vs. 4; p=0.02). There was otherwise no correlation between pathology and psychometric test scores.

Significance: Aβ plaques and pTau were uncommon in the resected brain tissue of patients who have undergone temporal lobectomy, and did not correlate with clinical characteristics or pre-operative psychometric test scores, except for a lower VPA median score in patients with Aβ plaques. Therefore, considering the low prevalence of Aβ plaques and pTau herein observed, it is unlikely that cognitive impairment in TLE is driven by the same mechanisms as in Alzheimer disease.

Keywords: cognitive decline, Aβ plaques, hyperphosphorylated tau, temporal lobectomy, histological assessment
1. Introduction

Temporal lobe epilepsy (TLE) is one of the most common types of focal epilepsies. Among the pathological substrates recognised in TLE, hippocampal sclerosis (HS) is associated with a high rate of pharmacoresistance. In selected patients, anterior temporal lobectomy will render 60–85% seizure-free. The procedure involves resection of the epileptogenic anterior temporal lobe and mesial temporal structures.

The temporal lobe structures play a crucial role in higher cognition, most notably memory and language functions. Frequent seizures and the pathological changes in mesial temporal structures may result in deficits in cognition, which may increase the chance of developing dementia. Although progressive cognitive deterioration over time is recognized in TLE, particularly following temporal lobectomy, the mechanisms contributing to this decline are unknown.

Given that tangles of hyperphosphorylated tau (pTau) and amyloid (Aß) plaques are pathological hallmarks of Alzheimer disease (AD), these observations have led to speculation of their potential role in the cognitive decline seen in TLE patients. Thom, Liu, Thompson reported a post-mortem investigation of 138 patients with epilepsy and found Aß plaques in 34% and pTau in 69% of patients. Many patients had comorbidities, including learning deficit in 60%. The mean age of death was 56 years old and 35% of the patients died of sudden unexplained death in epilepsy (SUDEP). These characteristics likely reflected a very severe epilepsy phenotype and therefore might not represent the broader epilepsy population. Moreover, 30% of patients had a history of head injury and 44% had pathological evidence of traumatic brain injury (TBI), which might at least partly explain the high prevalence of pTau deposition given the well documented association of TBI with tau deposition in the brain.

In another study Tai, Koepp, Duncan investigated patients between 50 and 65 years old who underwent resective surgery for TLE. Aß plaques were found in the resected temporal cortex sections in only 5 of the 56 patients. The presence of pTau was reported in 93% of the patients, with 15% having moderate to severe pTau deposition which correlated with a decline in cognitive tests performance 1-year post-surgery. However, when compared to an age matched control population of post-mortem cases from the literature, the prevalence of moderate to severe pTau pathology was not statistically different. Given the
association between age and pTau deposition, these findings might be attributed to the age of the patients studied rather than their underlying epilepsy phenotype.

It remains unclear whether these reported pathological changes are an epiphenomenon in an age group that has increased risk of AD (and the presence of AD pathologies), or are related to epilepsy and the presence of recurrent seizures, and whether they contribute to the cognitive deficits seen in many patients with chronic TLE. In this study, we aimed to investigate the prevalence of pTau and Aβ plaques in the resected hippocampus and temporal cortex in patients with drug-resistant TLE across a broad age range, and to correlate the pathological changes with pre-operative psychometric assessments.

2. Methods

2.1. Patient selection and clinical data

Eligible patients were retrospectively selected from the epilepsy surgery register of the Royal Melbourne Hospital, Melbourne, Australia, from 1993 to 2017. Patients with drug-resistant TLE who underwent anterior temporal lobectomy with histologically confirmed HS or without identified pathology, and who had pre-surgical psychometric testing, were eligible for inclusion. Patients without available paraffin blocks containing the brain tissue, or results of the specified psychometric testing instruments, or who had a pre-operative diagnosis of AD, were excluded. All patients provided written informed consent. The study was approved by The Melbourne Health Human Research Ethics Committee (Project No 2005.243).

The clinical history and demographic data of each patient was retrieved from medical records. Recorded information relevant to this study included age at onset of epilepsy, duration of epilepsy, side of surgery and handedness, pre-operative psychometric testing, seizure types and frequency and history of head injury.

2.2. Cognitive assessments

At our centre patients with drug-resistant TLE referred for consideration of resective surgery routinely undergo pre-surgical evaluation by a board-certified clinical neuropsychologist. The evaluation includes a formal psychometric examination with cognitive tests tailored to the individual patient’s clinical profile. For the purpose of this study three tests for verbal and visual learning were selected for analysis because of their sensitivity to temporal lobe pathology. These tests are the Rey Auditory Verbal Learning Test (RAVLT), Verbal Pair Associates (VPA) Test and Rey Complex Figure Test (RCFT). RAVLT total score is a measure of verbal supra-span learning. In this test patients are
presented with a list of 15 words and asked to recall them immediately. This is repeated five times and the RAVLT total score is the sum of words successfully recalled across all trials. Delayed verbal recall was measured using the long delay free-recall score (RAVLT A7), which represents the number of words recalled after a delay of 20-30 minutes.

VPA Test, from the Wechsler Memory Scale – Revised, examines the more fundamental aspects of verbal memory. The patient is first presented with 8 word-pairs and then given one of the words and asked to recall the word it was paired with. Four of the word-pairs are ‘easy’ (pairs of semantically related words) and four are ‘hard’ (semantically unrelated words). Three trials of the word-pairs are presented, resulting in a learning score between 0-12 for each of the easy and hard pairs. Arbitrary associative learning, as measured by the semantically unrelated pairs, has been shown to be a sensitive marker of mesial temporal pathology in epilepsy and related disorders.

RCFT provides a measure of delayed visual recall, and involves copying a complex figure and then reproducing it from memory after a delay of 20-30 minutes.

2.3. Immunohistochemistry for phosphorylated tau and amyloid

Formalin-fixed, paraffin-embedded tissue blocks from the recruited patients were retrieved from the pathology archives. Blocks containing temporal cortex and hippocampus were selected for immunohistochemical analysis according to anatomical position, best preserved tissue, and representative pathology. The selection was carried out by reviewing previously prepared hematoxylin & eosin stained sections representative of each block. HS was classified according to guideline by the International League Against Epilepsy (ILAE).

Type I refers to severe neuronal loss and gliosis mainly in both the CA1 and CA4 regions, type II is a pathology predominant in CA1, and in type III the pathology is predominantly found in CA4.

Immunohistochemistry for pTau and Aβ plaques was carried out on 7-μm thick paraffin-embedded sections mounted on charged slides. The staining for pTau was performed using the automated immunostainer DAKO Autostainer with the primary antibody anti-AT8 (1:1000, DAKO, Santa Clara, USA), following the manufacturer’s instruction. The Aβ staining was performed manually using the 1E8 primary antibody (1:4000), kindly provided by Dr. Qiao-Xin Li, Florey Institute of Neurosciences, Melbourne, Australia. Sections were deparaffinized with xylene, rehydrated in graded solutions of ethanol (100%, 95% and 50%) and washed in distilled water. Hydrogen peroxide was used to quench endogenous peroxidase...
activity and then slides were immersed in a solution of 90% formic acid for antigen retrieval. Sections were incubated with primary antibody in Tris-HCl buffer for 1 hour at room temperature in a humidified chamber, followed by incubation with biotinylated antimouse/rabbit immunoglobulins for 10 min and peroxidase conjugated streptavidin also for 10 min (LSAB+ kit, DAKO, Santa Clara, USA). 3,3'-diaminobenzidine tetrahydrochloride (DAB, DAKO, Santa Clara, USA) was used as the chromogen substrate and sections were counterstained with hematoxylin (DAKO, Santa Clara, USA). After dehydration through sequential washes with increasing ethanol concentrations and finally in xylene, slides were cover slipped with DPX mounting medium. Slides from a confirmed case of AD were obtained from the Victorian Brain Bank (Application No 18.18) and used as a positive control for each staining run. All sections were analyzed using a light microscope.

2.4. Phosphorylated tau and Aβ amyloid pathology analysis

Because none of the tissue sections had widespread pTau pathology we did not use the Braak staging for quantification. Instead, pTau and Aβ amyloid burden were assessed semi-quantitatively with scores of none (score=0), sparse (<3 plaques or pTau positive neurons/100x microscopic field, score=1), moderate (3-6, score=2) or frequent (>6, score=3), as defined in the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) 26. Temporal cortex and hippocampus sections were analysed and scored separately; the higher score was used in statistical analysis. Scoring of sections was carried out by one observer (J.C.S.) and reviewed by an experienced neuropathologist (C.M.), blinded to the clinical information. Patients who had evidence of amyloid plaques, regardless of the score or location, were collectively termed “amyloid positive group” (Amyloid +), and the patients with no pathological evidence were termed “amyloid negative group” (No amyloid).

2.5. Data analysis

Spearman’s correlation coefficient was used to examine the relationship between the presence of Aβ plaques and pTau and the clinical data, including age at surgery, epilepsy onset and duration, side of resection, history of head injury and occurrence of focal to bilateral tonic-clonic seizures. The Mann-Whitney U test was used to compare cognitive test scores between patients with and without Aβ plaques. P values of <0.05 were considered statistically significant. All statistical analysis was performed using Stata version 16 (StataCorp, TX).
3. Results

3.1. Clinical characteristics

A total of 128 patients underwent anterior temporal lobectomy at The Royal Melbourne Hospital from 1993 to 2017. Both brain tissue sections and neuropsychometric test results were available for 56 patients, who were included in this analysis. Their clinical characteristics are summarized in Table 1 and details are provided in Supplementary Table 1. Their age at surgery ranged from 20 to 68 years, with the majority under 50 (n=48, 86%). Most had histologically confirmed HS (n=51, 91%), of these 10 were classified as ILAE type I, five were type II, one was type III, and 35 were not subclassified.

3.2. Amyloid-β plaques and hyperphosphorylated tau

Paraffin blocks containing hippocampal tissue were available for all 56 patients while temporal cortex blocks were available for 40. Diffuse Aβ plaques were present in 4 of the 56 patients (7%) and all had plaques considered ‘moderate’ (3-6 plaques/100x microscopic field; Figure 1A). 2 out of these 4 amyloid positive patients were under 50 years old (50%). Diffuse Aβ plaques were present only in the temporal cortex section for 3 patients and in both the temporal cortex and hippocampus for 1. The presence of Aβ plaques was not associated with age of onset of epilepsy, duration of epilepsy, side of resection, history of head injury, or history of focal to bilateral tonic-clonic seizures (Figure 2A-C).

Only 2 patients had sparse scattered pTau positive neurons (Figure 1B). Both patients also had moderate amyloid plaques. Neurofibrillary tangles of pTau were found only in the temporal cortex section of these patients, not on the hippocampus section.

Table 2 presents a comparison of the findings between this study and previous studies that analysed Aβ plaques and pTau in resected temporal cortex tissues. Our cohort had a prevalence of Aβ plaques (7%) lower than the previous two studies of Thom, Liu, Thompson and Tai, Koepp, Duncan (34% and 15%, respectively). However, our patient population was younger compared to these two studies, with 86% of patients being younger than 50 years old. While both studies reported widespread pTau in temporal cortex tissues, this was not observed to the same extent in our patients.

3.3. Association between cognitive function and Aβ amyloid pathology

A summary of the psychometric testing scores and clinical characteristics of the 4 amyloid positive patients can be found in Table 3. There was no correlation between performance in the pre-surgical psychometric testing and presence of Aβ plaques (Figure 2D-
E). However, we observed that the amyloid positive group had a lower median score for the VPA hard assessment of verbal memory compared to the amyloid negative group (0 compared to 4; p=0.02).

The two patients who had both scattered pTau and widespread amyloid plaques had different cognitive profiles. Patient P3 (61 years old, male) who presented moderate Aβ plaques in both temporal cortex and hippocampus scored poorly on verbal memory (<2SD for VPA easy and <1SD for hard) and visual learning test (<1SD for RCFT delay). While Patient P16 (50 years old, female) who did not have Aβ plaques in the hippocampus, only in the temporal cortex section, scored within normal limits in the same tests. Data for RAVLT total and A7 was not available for these patients.

4. Discussion

In the present study, widespread pTau and Aβ plaques were rarely seen in the epileptogenic temporal lobe tissues resected from patients with drug resistant TLE. Amyloid pathology was not associated with the clinical characteristics of epilepsy including duration, side and age of onset of epilepsy. The presence of Aβ plaques did not correlate with pre-operative cognitive impairment except for a lower median score in the VPA hard assessment in patients with Aβ plaques.

In this study, the presence of Aβ plaque deposition did not correlate with older age at the time of surgery or longer duration of epilepsy. Amyloid plaques have been found in both epilepsy patients and age-matched healthy controls. A study with TLE patients (30-61 years old) who underwent temporal lobe resection surgery found a similar prevalence of Aβ plaques to our study, 10 out of 101 patients, which correlated with older age 27. The study also reported the presence of plaques in 32% of the 406 autopsy controls (30-92 years old) without dementia or epilepsy 27. Recently, elevated levels of the amyloid precursor protein (APP) were found in the hippocampus of TLE patients and APP was shown to be preferentially processed through the amyloidogenic pathway, although its cleavage product amyloid-β was not associated with reduced cognitive performance. Sparse Aβ plaques were also detected in 3 of 11 patients (27%) and only 1-3 plaques were reported for each individual by Gourmaud, Shou, Irwin 28. Collectively, these observations suggest that Aβ plaques can develop in individuals with or without a history of epilepsy at a similar rate. Moreover, this accumulation is not necessarily accompanied by impaired cognitive performance.
A report of patients with childhood epilepsy followed up for over 50 years found a higher frequency (22%, 9/41) of amyloid plaque deposition on PiB-PET imaging compared to healthy controls (7%, 3/46). However, the authors did not find a correlation between amyloid plaque deposition and cognitive impairment in the cross-sectional analysis which corroborates our findings. Our current understanding of what constitutes “normal” amyloid deposition and its impact in cognition in the general population remains limited. It has been reported that 20-30% of healthy people aged between 65 and 90 years show significant amyloid deposition in plaques and can still be cognitively normal. A recent study showed that amyloid detected by cerebrospinal fluid levels was associated with memory variability in cognitively healthy individuals aged between 65 and 73, although hippocampal atrophy seemed to be the main contributor.

In the studies of Tai, Koepp, Duncan and Thom, Liu, Thompson, the severity of pTau pathology was associated with progressive cognitive decline after surgery, but there was no correlation between severity and pre-operative neuropsychometric test scores. However, in both studies this association might be related to ageing effect. pTau deposition is highly associated with older age. The patients studied by Tai, Koepp, Duncan were between 50 and 65 years old and pTau was present in 93%, although the majority was classified as mild (Braak I/II). In the post-mortem study of Thom, Liu, Thompson, the mean age at death for Braak stage 0 was 35 years old compared to 70 years old in Braak stage V. In our study, we did not observe the same extent of pTau deposition.

However, a few other studies that investigated tau pathology in younger patients with drug resistant epilepsy have reported increased levels of pTau. Puvenna, Engeler, Banjara identified levels and patterns of expression of pTau in TLE patients (4 months-58 years, mean age 27.6 years) similar to patients with chronic traumatic encephalopathy (CTE; 50-96 years, mean age 73.3 years). However, there was no difference in the mean severity score of pTau in TLE patients when compared to healthy controls, whereas the mean score in CTE patients was higher. In this study, 8 out of 19 were children and 4 were infants, therefore this is a cohort with more severe epilepsy than ours, which may not be representative of the broader epilepsy population. There was also no information on whether the presence of tau pathology was associated with cognitive deficits or other clinical factors.

Another study from Smith, Blessing, Parisi found pTau pathology in 38% of patients with drug resistant epilepsy who underwent resective surgery between 23 to 39 years old (median age 29.5 years). Despite the higher prevalence of tau burden in this younger cohort, there was no correlation of tau pathology with pre- or post-operative cognitive test.
scores. In contrast, Gourmaud, Shou, Irwin \(^{28}\) reported not only increased expression of pTau in epilepsy patients aged between 20 and 56 (mean age 35.6), but also a negative correlation between total tau, pTau, and pre-operative executive function. Although prevalence of pTau was higher in these studies compared to ours, all 3 reported only diffuse somatic pTau reactivity in neurons and not neurofibrillary tangles as seen in AD, CTE and other neurodegenerative diseases. The pattern of tau accumulation and incidence of tau burden in epilepsy is not yet clear and varies greatly between studies and therefore there is not enough evidence to support the notion that cognitive decline in epilepsy has the same underlying mechanism as in AD.

There is strong evidence that verbal arbitrary associative learning is a proximal marker of mesial temporal pathology, and might be a neurocognitive endophenotype of temporal lobe epilepsy \(^9\). In our study, the presence of Aß plaques did not correlate with pre-operative scores of verbal and visual learning. However, we observed that the VPA hard test score was lower in the TLE amyloid positive group (0 vs. 4). In a previous study that recorded single neurons in the mesial temporal lobe of patients while being tested for remembering pairs of words, the activity of the entorhinal cortex reflected the capacity of successfully recalling the pairs \(^{23}\). Therefore, an accumulation of Aß plaques in this area could be a contributor for the lower performance in the VPA hard test. The test used to examine visual memory, the RCFT, is one of the most common tests to evaluate visuospatial skills in neuropsychological assessments of elderly people and has been considered effective in discriminating AD stages \(^{35, 36}\). However, in our study, we found that the epilepsy associated cognitive impairment was independent of amyloid pathology. Therefore, it is unlikely that cognitive impairment in TLE is driven by the same mechanisms as in AD.

Our study has limitations. Although immunostaining is an accepted method to identify pathological abnormalities in the brain its analysis is an indirect measure and rely on the expertise of the neuropathologist. A common limitation of retrospective studies of human brain specimens, including ours, is the lack of fresh tissues for additional molecular analysis that could help better quantify and understand the mechanisms underlying the complex AD pathology. Finally, given the relatively small number of cases with pathology, the observed lower VPA median score in patients with Aß plaques should be interpreted with caution.

In conclusion, our study found that pTau burden and Aß plaque deposition were uncommon in resected temporal lobe tissues in patients with chronic drug-resistant TLE. The prevalence and severity of Aß plaques did not reflect an impairment in overall pre-operative verbal and visual learning and was also not correlated with longer duration of epilepsy.
Extended follow up, in particular of the patients with high levels of amyloid plaques, is necessary to further understand the effect of this pathology on long-term cognitive function and its interaction with seizure control.

5. References


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Key points box

- Both Aβ plaques and pTau were uncommon in patients undergoing surgery for drug-resistant temporal lobe epilepsy.
- pTau was found in patients over 50 years old and very occasionally across brain sections. Diffuse Aβ plaques were found in only 7% of patients at moderate severity.
- The pathology did not correlate with clinical history of epilepsy, including age of onset and duration of epilepsy.
- Pathology also did not correlate with pre-operative psychometric tests, except for a lower median score in verbal memory observed in patients with Aβ plaques.
- Aβ plaques and pTau are unlikely to be the underlying cause of cognitive impairment in drug-resistant temporal lobe epilepsy.

Disclosure of conflicts of interest
None of the authors has any conflict of interest to disclose.

Ethical publication statement
We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Figure 1. Sections of temporal neocortex of a patient with moderate amyloid-β plaques stained with 1E8 antibody (A) and sparse scattered hyperphosphorylated tau tangles stained with AT8 antibody (B). Scale bar = 100 μm.

Figure 2. Box-plots representing the distribution of clinical characteristics (A-C) and pre-operative psychometric test scores (D-F) between patients with Aβ plaques (Amyloid +) and no Aβ plaques. Patients with Aβ plaques had a lower median score in the VPA hard
test (Mann-Whitney; *P=0.02). Red dots represent patients with pTau and bars represent median of the distribution.
Table 1. Clinical characteristics of the patient population studied (total n=56).

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Number of patients for whom data was available</th>
<th>Median (range) or proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex - female, n (%)</td>
<td>56</td>
<td>31 (55%)</td>
</tr>
<tr>
<td>Age at surgery, median (range)</td>
<td>56</td>
<td>34 (20 - 68)</td>
</tr>
<tr>
<td>Age of onset of epilepsy, median (range)</td>
<td>54</td>
<td>15 (0 - 56)</td>
</tr>
<tr>
<td>Duration of epilepsy in years, median (range)</td>
<td>54</td>
<td>20 (1 - 56)</td>
</tr>
<tr>
<td>Side of resection - right, n (%)</td>
<td>56</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Handedness - right, n (%)</td>
<td>49</td>
<td>39 (79%)</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>56</td>
<td>51 (91%)</td>
</tr>
<tr>
<td>History of focal to bilateral tonic-clonic seizures, n (%)</td>
<td>35</td>
<td>31 (88%)</td>
</tr>
<tr>
<td>History of head injury, n (%)</td>
<td>56</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>RAVLT total</td>
<td>31</td>
<td>44 (21 - 62)</td>
</tr>
<tr>
<td>RAVLT A7</td>
<td>31</td>
<td>8 (0 - 15)</td>
</tr>
<tr>
<td>VPA easy</td>
<td>48</td>
<td>9.1 (2 - 12)</td>
</tr>
<tr>
<td>VPA hard</td>
<td>48</td>
<td>3.7 (0 - 10)</td>
</tr>
<tr>
<td>RCFT delay</td>
<td>52</td>
<td>12 (0 - 27)</td>
</tr>
</tbody>
</table>

[Rey Auditory Verbal Learning Test (RAVLT), Verbal Pair Associates (VPA) Test and Rey Complex Figure Test (RCFT)]
Table 2. Comparison between findings from the present study and previous reports of incidence of amyloid and tau pathology in epilepsy patients.\(^{17,19}\)

<table>
<thead>
<tr>
<th></th>
<th>Present study (n=56)</th>
<th>Tai 2016 (n=33)</th>
<th>Thom 2011 (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range, years</strong></td>
<td>20-68</td>
<td>50-65</td>
<td>15-96</td>
</tr>
<tr>
<td><strong>Amyloid plaques</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (7%)</td>
<td>5 (15%)</td>
<td>47 (34%)</td>
</tr>
<tr>
<td>Sparse</td>
<td>0</td>
<td>3 (9%)</td>
<td>19 (14%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (7%)</td>
<td>1 (3%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Frequent</td>
<td>0</td>
<td>1 (3%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td><strong>Tau pathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2 (3%)</td>
<td>31 (93%)</td>
<td>95 (68%)</td>
</tr>
<tr>
<td>Mild/Braak I, II</td>
<td>2 (3%)</td>
<td>26 (78%)</td>
<td>50 (36%)</td>
</tr>
<tr>
<td>Moderate/Braak III, IV</td>
<td>0</td>
<td>4 (12%)</td>
<td>42 (30%)</td>
</tr>
<tr>
<td>Severe/Braak V</td>
<td>0</td>
<td>1 (3%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>
Table 3. Cognitive test scores of patients with Aβ plaques.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Hippocampal Aβ plaques</th>
<th>Temporal cortex Aβ plaques</th>
<th>pTau</th>
<th>VPA easy</th>
<th>VPA hard</th>
<th>RCFT delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3</td>
<td>61</td>
<td>M</td>
<td>Moderate</td>
<td>Moderate</td>
<td>TC only</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>P16</td>
<td>55</td>
<td>F</td>
<td>-</td>
<td>Moderate</td>
<td>TC only</td>
<td>11</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>P18</td>
<td>36</td>
<td>F</td>
<td>-</td>
<td>Moderate</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>13.5</td>
</tr>
<tr>
<td>P26</td>
<td>38</td>
<td>M</td>
<td>-</td>
<td>Moderate</td>
<td>-</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[Male (M), Female (F), Temporal Cortex (TC), Verbal Pair Associates (VPA) Test and Rey Complex Figure Test (RCFT)]
A | Amyloid-β (1E8)

B | pTau (AT8)

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