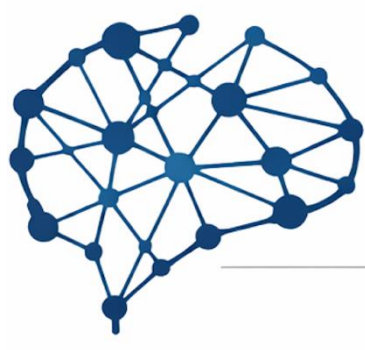


Neurodegenerative Histopathology and Cognitive Features in Drug-Resistant Mesial Temporal Lobe Epilepsy: A Systematic Review



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- AD pathology is uncommon in MTLE-DR; however, a subset of patients fulfills the histopathological criteria for AD, which is associated with poorer cognitive performance.
- Nearly half of the cohort exhibited phosphorylated tau pathology in the absence of amyloid deposition.
- Most previous studies have characterized AD-related histopathological changes in comparison with other proteinopathies.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Cognitive outcomes following surgery for drug-resistant mesial temporal lobe epilepsy (MTLE-DR) are heterogeneous and difficult to predict. While hippocampal sclerosis is the canonical epileptogenic substrate, resected mesial temporal tissue frequently demonstrates Alzheimer’s disease (AD)-related proteinopathies, suggesting the presence of mixed pathology comorbidities. The contribution of coexisting epileptic and neurodegenerative pathology to cognitive vulnerability in MTLE-DR remains poorly defined. We systematically evaluated the frequency of AD-related histopathology and its relationship with cognitive performance in surgically treated MTLE-DR.	We conducted a PRISMA 2020-compliant systematic review (PROSPERO CRD42024613136). MEDLINE (PubMed), Web of Science, Scopus, and Google Scholar were searched between October 2024 and May 2025 for MTLE-DR surgical cohorts reporting histopathological assessment of phosphorylated tau (p-tau) and/or beta-amyloid (Aβ) alongside neuropsychological outcomes. Two reviewers independently screened studies and extracted data. Frequencies of neurodegenerative comorbid pathology were synthesized, and reported associations with cognitive domains were summarized.	Four studies (three cross-sectional, one retrospective cohort) met inclusion criteria. Disaggregated patient-level data were available for 111 patients (median age 42.9 years; 53.2% female). Hippocampal sclerosis was present in 92.8% (type 1: 78.4%; type 2: 14.4%). Evidence of neurodegenerative comorbid pathology was identified in 48.6% of patients, with biomarker profiles distributed as p-tau–/Aβ– (49.5%), p-tau+/Aβ– (42.3%), p-tau+/Aβ+ (6.3%), and p-tau–/Aβ+ (1.8%). Compared with patients without neurodegenerative pathology, those with isolated p-tau accumulation were older (53.6 ± 4.2 vs 36.9 ± 11.9 years) and had longer epilepsy duration (31.9 ± 19.4 vs 20.8 ± 13.8 years). Biomarker status was not associated with sex, side of resection, or hippocampal sclerosis subtype. Despite heterogeneous cognitive assessments, memory outcomes varied significantly by mixed pathology profile, with visual memory most affected ($\chi^2 = 22.86$, $p < 0.001$), particularly in p-tau+/Aβ– cases. Verbal memory also differed across pathology groups ($\chi^2 = 14.82$, $p = 0.022$), while attention did not.	Mixed pathology comorbidities—specifically the coexistence of hippocampal sclerosis and AD-related tau pathology—are common in MTLE-DR and are associated with memory impairment. These findings support a comorbid disease model in which neurodegenerative pathology contributes to cognitive vulnerability in epilepsy, with potential implications for surgical prognosis, cognitive counseling, and long-term dementia risk assessment	Toscano ECB, Vieira ÉLM, Grinberg LT, Rocha NP, Brant JAS, Paradelo RS, Giannetti AV, Suemoto CK, Leite REP, Nitrini R, Rachid MA, Teixeira AL. Hyperphosphorylated Tau in Mesial Temporal Lobe Epilepsy: a Neuropathological and Cognitive Study. Mol Neurobiol. 2023;60(4):2174-2185. doi: 10.1007/s12035-022-03190-x Silva JC, Vivash L, Malpas CB, Hao Y, McLean C, Chen Z, O'Brien TJ, Jones NC, Kwan P. Low prevalence of amyloid and tau pathology in drug-resistant temporal lobe epilepsy. Epilepsia. 2021;62(12):3058-3067. doi: 10.1111/epi.17086 Gourmaud S, Shou H, Irwin DJ, Sansalone K, Jacobs LM, Lucas TH, Marsh ED, Davis KA, Jensen FE, Talos DM. Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy. Brain. 2020 Jan 1;143(1):191-209. doi: 10.1093/brain/awz381. Erratum in: Brain. 2020;143(3):e24. doi: 10.1093/brain/awaa007 Tai XY, Koeppe M, Duncan JS, Fox N, Thompson P, Baxendale S, Liu JY, Reeves C, Michalak Z, Thom M. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain. 2016 Sep;139(Pt 9):2441-55. doi: 10.1093/brain/aww187 Contact: ramiro.ruiz@innn.edu.mx FIGURES IN QR  ALZHEIMER'S ASSOCIATION AAIC>26