

TREM2/DAP12-driven Microglial Responses Are Associated With Tau Burden And Cognitive Impairment In Temporal Lobe Epilepsy

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Drug-resistant temporal lobe epilepsy was associated with increased hippocampal p-tau burden, microglial activation, and upregulation of the TREM2/DAP12 signaling axis, without amyloid- β or TDP-43 depoistion. Microglial markers were associated with executive dysfunction and positively correlated with p-tau accumulation. The findings support a mechanistic link between TLE, neuroinflammation, tau pathology and cognitive impairment.

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

REFERENCES

Temporal lobe epilepsy (TLE) is the most common cause of drug-resistant epilepsy in adults. Seizures predominantly originate from the mesial temporal lobe and are accompanied by cognitive impairment, involving memory and learning. Increasing evidence supports shared pathophysiological mechanisms between TLE and Alzheimer’s disease (AD), including chronic neuroinflammation and tau-related neurodegeneration. Microglial activation is a central feature of both conditions, and the triggering receptor expressed on myeloid cells 2 (TREM2) and its adaptor protein DAP12 form a key signaling axis regulating microglial activation, phagocytosis, and inflammatory responses. However, the role of the TREM2/DAP12 pathway in TLE-associated neurodegeneration remains poorly understood. This study aimed to investigate the involvement of the TREM2/DAP12 pathway in neurodegenerative processes associated with drug-resistant TLE and its relationship with cognitive impairment and hyperphosphorylated tau (p-tau) burden.

Table 1. Sociodemographic and clinical characteristics of participants (n = 40)

	Control (n=20)	TLE (n=20)	p value
Sex, n (%) *			
Male, n (%)	13 (65)	9 (45)	0.341
Female, n (%)	7 (35)	11 (55)	
Age (years), mean (SD) **	44.15 $\pm$ 7.54	40.95 $\pm$ 7.88	0.198
Educational level (years), mean (SD)	--	7 $\pm$ 3.14	--
Epilepsy onset (years), mean (SD)	--	3 $\pm$ 3.61	--
Duration of epilepsy (years), mean (SD)	--	36 $\pm$ 11.31	--
Seizure type, n (%)			--
Generalized		2 (10)	
Focal	--	18 (90)	
Focal impairment awareness		13 (65)	
Focal to bilateral tonic clonic		4 (20)	
Frequency of seizure (monthly), mean (SD)	--	4 $\pm$ 4.08	--
HS laterality			--
Right, n (%)	--	11 (55)	
Left, n (%)		9 (45)	
Hippocampal sclerosis			--
HS type 1, n (%)		13 (65)	
HS type 2, n (%)	--	6 (30)	
HS type 3, n (%)		1 (5)	

* Fisher’s exact test; ** t-test; TLE: Temporal lobe epilepsy; SD: standard deviation; HS: hippocampal sclerosis; N/A: not applicable.

Patients with drug-resistant TLE undergoing selective hippocampectomy were subjected to comprehensive neuropsychological assessments evaluating executive functions, memory, and language. Surgically resected hippocampal specimens were analyzed by immunohistochemistry to assess the expression of neurodegenerative proteins (p-tau, amyloid- β 1-42, and TDP-43) and microglial markers (Iba-1, CD68, TREM2, and DAP12). Quantitative analyses were performed across hippocampal subfields and compared with age-matched control hippocampi (n = 20 per group). Associations between microglial markers, cognitive performance, and p-tau burden were examined.

Sociodemographic and clinical characteristics of the participants are described in Table 1. TLE patients had increased p-tau expression across all hippocampal subregions, with neuronal cytoplasmic accumulation displaying tangle and pretangle patterns. No pathological deposition of amyloid- β or TDP-43 was detected. Iba-1 and CD68 expression were increased throughout the hippocampus, indicating widespread microglial activation. TREM2 expression was elevated in the CA1 region and subiculum, whereas DAP12 expression was increased in CA1, dentate gyrus, and subiculum (Figure 1). Linear regression demonstrated that higher levels of CD68, TREM2, and DAP12 were associated with executive function impairment (Table 2). Additionally, hippocampal levels of Iba-1, CD68, and TREM2 showed a positive correlation with p-tau burden.

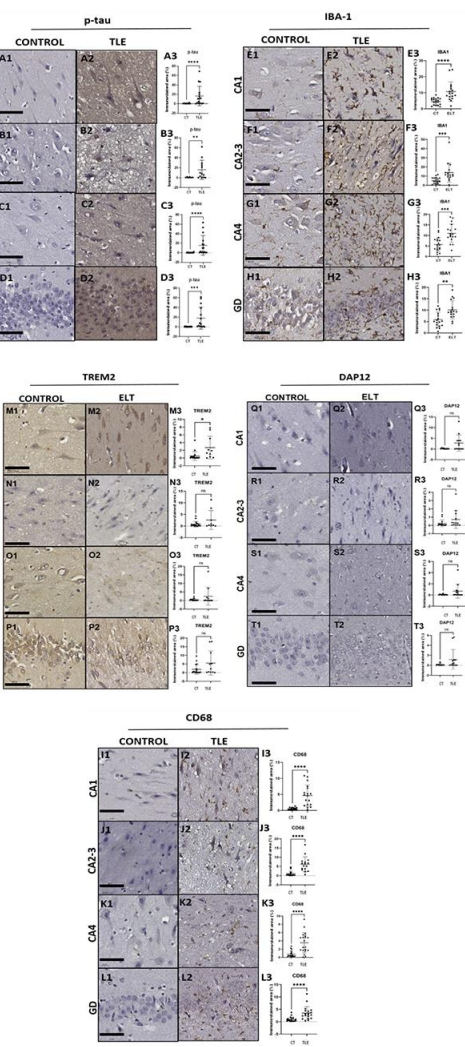


Figure 1 - Representative photomicrographs and quantitative analysis of p-tau pathology and microglial markers across hippocampal subregions in TLE patients compared to age-matched controls. The figure shows immunohistochemical staining for p-tau (red) and microglial markers Iba-1 (green), CD68 (green), TREM2 (green), and DAP12 (green) in CA1, CA2-3, CA4, and DG subregions. Quantitative analysis shows increased p-tau and microglial marker expression in TLE patients compared to controls.

Table 2. Association between the cognitive performance and expression of microglial proteins.

Cognitive test	Marker	Hippocampal area	β	95% CI	p value
Trail A	CD68	CA1	-0.204	-0.728; 0.191	0.259
		CA2-3	-0.026	-0.496; 0.439	0.903
		CA4	-0.122	-0.333; 0.090	0.217
		DG	-0.028	-0.332; 0.141	0.862
		SD	-0.017	-1.172; 0.979	0.997
Trail B	TREM2	CA1	-0.607	-1.496; -0.215	0.007
		CA4	-0.264	-0.743; 0.215	0.255
		DG	-0.174	-1.336; 0.987	0.750
		CA2-3	-0.027	-0.423; 0.369	0.854
		SD	0.040	-0.032; 0.094	0.726
Trail C	DAP12	CA1	0.054	-0.062; 0.170	0.329
		DG	0.119	-0.067; 0.305	0.188
		CA2-3	0.040	-0.750; 0.827	0.561
		CA4	-0.097	-0.715; 0.543	0.451
		SD	-0.102	-0.329; 0.114	0.342
Trail D	CD68	CA1	-0.173	-0.538; -0.207	0.001
		CA2-3	0.064	-1.306; 1.437	0.931
		CA4	-0.477	-1.149; -0.246	0.010
		DG	-0.144	-0.602; 0.315	0.515
		SD	-0.007	-1.260; 1.246	0.952
Trail E	TREM2	CA1	-0.415	-0.685; -0.144	0.006
		CA2-3	0.028	-0.026; 0.082	0.285
		CA4	0.020	-0.109; 0.148	0.744
		DG	0.044	-0.176; 0.259	0.429
		SD	-0.106	-0.376; -0.015	0.036
Trail F	CD68	CA1	0.102	-0.090; 1.254	0.796
		CA4	-0.052	-0.178; 0.074	0.389
		DG	-0.115	-0.247; -0.003	0.040
		CA2-3	-0.040	-1.092; 0.912	0.9074
		SD	-0.106	-0.546; -0.113	0.009
Trail G	TREM2	CA1	-0.106	-0.546; -0.113	0.009
		CA2-3	-0.040	-1.092; 0.912	0.9074
		CA4	-0.106	-0.546; -0.113	0.009
		DG	-0.115	-0.247; -0.003	0.040
		SD	-0.203	-1.307; 0.901	0.710

CA: Cereb. Anterior; CI: confidence interval; DG: dentate gyrus; DAP12: DNAX-activating protein of 12 kDa; SD: subiculum; TREM2: Triggering Receptor Expressed on Myeloid Cells 2.

Dysregulation of the TREM2/DAP12 axis is associated with tau pathology, neuroinflammation, and cognitive impairment in drug-resistant TLE, reinforcing mechanistic parallels with AD and highlighting TLE as a risk factor for dementia.



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