Astrocyte Reactivity in Alzheimer's Disease: Implications for Blood-Brain Barrier permeability

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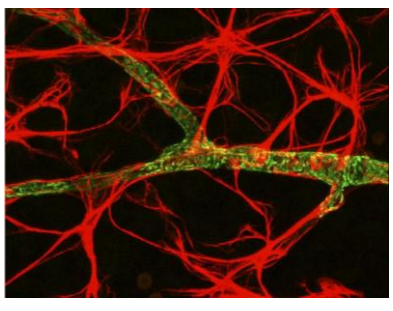
Introduction

Astrocytes undergo structural and metabolic changes in Alzheimer's disease (AD) progression. These changes impact functions such as blood-brain-barrier (BBB) support(1), can be traced using biomarkers like CSF Glial Fibrillary Acidic Protein (GFAP) and lactate, and may vary by APOE genotype(2). This study examines the relationship between these astrocytic biomarkers and **BBB permeability in AD**, considering the effects of APOE genotype.



Astrocyte processes (visualized with antibodies against GFAP, red) make contacts with capillaries throughout the CNS.

Adapted from:
https://doi.org/10.1152/physrev.00041.2013

Materials and Methods

Between January and June 2024, we enrolled **98 patients** with biomarker-confirmed AD and 17 age-matched healthy controls (HC). CSF GFAP and Lactates, albumin quotient (Qalb) and APOE genotyping were measured. AD patients were subclassified as **APOE-ε4** when carrying at least one ε4 allele (n=49), as APOE-ε3 otherwise (n=49). We performed Kruskal-Wallis tests and multivariate regressions to verify the associations of CSF GFAP and Lactates with Qalb, adjusting for age, sex and p-tau.

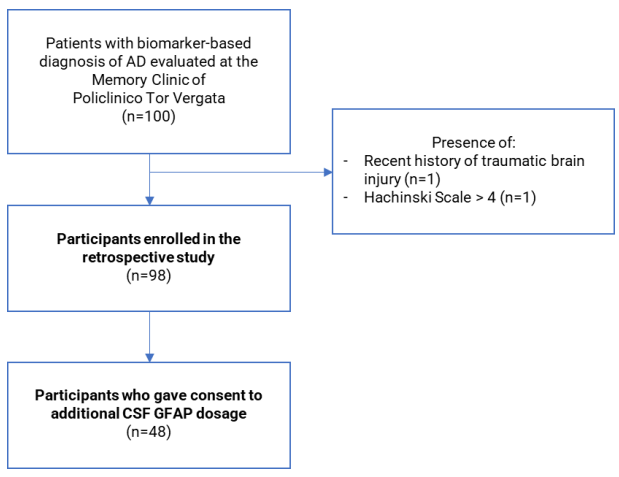


Figure 1. Flowchart summarizing enrolment procedures for the present study

Results

There were no significant differences in terms of Qalb nor CSF levels of astrocytic biomarkers across subgroups, and BBB was intact throughout (Table 1).

	HC (n=17)	APOE ε3 (n=49)	APOE ε4 (n=49)	Test Statistics	p
Age (yo)	64.00 ± 15.75	71.78 ± 6.70	72.43 ± 7.28	4.672	0.097
Sex (%F)	41.18%	48.98%	48.00%	0.320	0.852
MMSE	28.00 ± 1.25	23.68 ± 3.05	23.74 ± 4.01	35.624	**<.001*** **
CSF Aβ42 (pg/ml)	1046.36 ± 415.34	435.04 ± 130.13	457.92 ± 114.27	36.517	**<.001*** **
CSF p-tau (pg/ml)	34.18 ± 14.79	121.32 ± 41.14	119.21 ± 46.28	38.374	**<.001*** **
CSF t-tau (pg/ml)	227.71 ± 125.17	759.68 ± 352.57	737.15 ± 323.02	32.423	**<.001*** **
Qalb	6.27 ± 2.64	6.27 ± 3.10	5.27 ± 1.04	0.868	0.648
#CSF GFAP (pg/ml)	5.27 ± 1.04	6.27 ± 2.64	6.27 ± 3.10	1.446	0.485
CSF Lactates (pg/ml)	1.48 ± 0.39	1.49 ± 0.25	1.49 ± 0.32	0.422	0.802

Table 1. Comparisons of demographic features and CSF dosages between HC and AD patients stratified according to APOE genotype. HC: Healthy Controls; APOE: Apolipoprotein E; p: p-values; F: female; Qalb: Albumin Quotient; Bold values denote statistical significance; ***= p<.001; #CSF GFAP dosage was performed only in a subgroups of patients (APOE ε3: n=26; APOE ε4: n=22)

1. The adjusted analyses highlighted that **CSF GFAP** was negatively associated with Qalb in both APOE-ε3 (β=−0.495, p=0.016) and APOE-ε4 (β=−0.482, p=0.022). None of the predictors were associated with Qalb in HC (Table 2).

	HC (n=17)		APOE ε3 (n=26)		APOE ε4 (n=22)	
	β (std)	p	β (std)	p	β (std)	p
Age	0.536	0.151	−0.034	0.859	−0.028	0.884
Sex (F=1)	n.a.	0.688	n.a.	0.232	n.a.	**0.004****
CSF p-tau	−0.151	0.659	−0.217	0.275	−0.120	0.509
CSF GFAP	−0.098	0.782	−0.495	**0.016***	−0.482	**0.022***
	R^2=0.361		R^2=0.310		R^2=0.502	

Table 2. Multivariate regression analyses between CSF GFAP and Qalb.. HC: Healthy Controls; APOE: Apolipoprotein E; β=standardized; p: p-values; F: female; Bold values denote statistical significance

2. Conversely, **CSF Lactates** resulted moderately positively associated with Qalb values selectively in the APOE-ε4 subgroup (β=0.420, p=0.002). None of the predictors were associated with Qalb in APOE-ε3 (β=0.219, p=0.128) nor in HC (Table 3).

	HC (n=17)		APOE ε3 (n=49)		APOE ε4 (n=49)	
	β (std)	p	β (std)	p	β (std)	p
Age	0.614	0.097	−0.017	0.906	−0.221	0.090
Sex (F=1)	n.a.	0.867	n.a.	**0.023***	n.a.	**0.016***
CSF p-tau	−0.187	0.569	−0.019	0.899	0.008	0.948
CSF Lactates	−0.138	0.711	0.219	0.128	0.420	**0.002****
	R^2=0.367		R^2=0.151		R^2=0.301	

Table 3. Multivariate regression analyses between CSF Lactates and Qalb. HC: Healthy Controls; APOE: Apolipoprotein E; β=standardized; p: p-values; F: female; Bold values denote statistical significance

Discussion

Structural changes in AD reactive astrocytes, reflected by higher levels of GFAP, are associated with lower Qalb, which represents a more intact BBB. This is in line with previous finding revealing a link between astrocyte reactivity and restoration of junctional proteins (2), and might represent a **response to BBB impairment**, which holds detrimental effects in AD(3).

On the other hand, considering CSF Lactates a product of astrocytic metabolic activation, their increase alongside BBB disruption in APOE-ε4 patients might represent a genotype-specific **response to neuronal bioenergetic dysfunction**, possibly leveraging the astrocyte-neuron lactate shuttle.

Conclusion

These observations highlight the **diverse manifestations of reactive astrogliosis in AD, pointing at complex interactions with BBB permeability** and dynamic functional changes influenced by APOE genotype.

References

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