

Cerebrospinal fluid cytokine levels affect electroencephalographic activity in Alzheimer's disease

Journal of Alzheimer's

Disease Reports

Volume 9: 1–6

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DOI: 10.1177/25424823241306772

journals.sagepub.com/home/alr



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Abstract

To investigate the role of neuroinflammation as mediator of amyloid- β -induced cortical activity changes in Alzheimer's disease (AD), we examined the relationship between cerebrospinal fluid (CSF) inflammatory cytokines (IL-1 β , IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF- α , IFN- γ , GM-CSF, G-CSF, MIP-1 α , MCP-1) and electroencephalographic (EEG) abnormalities in a cohort of biologically defined AD patients ($n = 55$, M:F = 19:36, median age 73, Mini-Mental State Examination ≥ 22). We retrieved a positive association between IL-4 CSF levels and EEG background activity frequency; IL-7, IL-8, and IL-12 CSF levels were positively associated with the presence of interictal epileptiform discharges. Neuroinflammation accompanying AD pathology may enhance the amyloid's epileptogenic potential while also counter-acting neurodegenerative damage.

Keywords

Alzheimer's disease, cytokines, EEG, epileptiform activity, neuroinflammation

Received: 31 May 2024; accepted: 11 November 2024

Introduction

The deposition of amyloid- β (A β) oligomers in extracellular plaques is the hallmark pathological feature in all patients affected by Alzheimer's disease (AD), but the progression of neurodegeneration is not straightforward. Rather, it is constellated by predisposing or exacerbating factors, such as network hyperexcitability and epileptogenic processes, which could favor synaptic failure and cognitive decline.¹

Soluble A β oligomers possess a well-demonstrated epileptogenic potential, as they can disrupt neuronal glutamate uptake,² thereby altering synaptic plasticity and inducing changes in neuronal firing patterns.³ On the other hand, recent experimental evidence suggests that hyperexcitability itself may contribute to the progression of AD neuropathological burden.⁴ Specifically, seizure activity has been shown to activate microglia and astrocytes, leading to alterations in amyloid metabolism and to the synthesis of pro-inflammatory cytokines.⁵ Moreover, cytokine receptors located on neurons can modulate their excitability through ion channel modifications and the activation of various intracellular signaling pathways.⁶ This creates a self-perpetuating cycle, where AD pathology makes epileptiform activity more likely⁷ and cortical epileptiform

activity may in turn worsen AD pathology,⁸ with neuroinflammation serving as a crucial link between these two processes.

It is important to note that not all types of inflammation necessarily lead to seizures. Inflammation primarily acts as a defense mechanism and can be self-limiting, offering beneficial effects such as promoting A β clearance and the synthesis of neurotrophic growth factors.⁹ However, AD pathological processes can trigger aberrant neuroinflammation with harmful effects, such as the disruption of synaptic functioning and the induction of neuronal death.¹⁰

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Handling Associate Editor: Daniela Galimberti



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This evidence raises interest in the identification of specific patterns of neuroinflammation associated with abnormal cortical activity and synaptic dysfunction in AD. Therefore, in the present work we aimed at investigating the relationship between electroencephalographic (EEG) abnormalities—slowing of background activity and interictal epileptiform discharges (IED)—and the cerebrospinal fluid (CSF) levels of a panel of cytokines in a cohort of patients belonging to the AD continuum.¹¹

Methods

Subjects' enrolment

We enrolled sixty-one consecutive patients who had accessed the Memory Clinic of Policlinico Tor Vergata due to cognitive decline between March 2021 and February 2023. All patients fulfilled criteria for either amnesic mild cognitive impairment (MCI) (Mini-Mental State Examination (MMSE) score ≥ 24)¹² or early dementia due to AD (MMSE < 24).¹³ Upon CSF analysis, they all belonged to the biologically defined AD continuum¹¹ (i.e., CSF $A\beta_{42} < 600$ pg/mL).

We excluded patients with a history of epileptic seizures, recent ischemic stroke (within the last 6 months or radiological evidence of ischemic lesions), Hachinski score > 4 , chronic inflammatory/autoimmune conditions, signs and symptoms of ongoing infection, C Reactive Protein blood levels > 5.00 mg/L, and patients under antiseizure medications for reasons other than a diagnosis of epilepsy. Our sample eventually included 55 patients (male:female = 19:36; median MMSE score 23.9 (22.5–25.3); 27 patients with MCI and 28 patients with early dementia).

Ethics section

The study was conducted according to the Declaration of Helsinki and approved by the local ethical committee (protocol n°16/21).

CSF collection and analysis

Lumbar punctures and blood samples for complimentary analyses were performed as per standard internal procedures. CSF $A\beta_{42}$, p-tau and t-tau concentrations were determined using a sandwich enzyme-linked immunosorbent assay (EUROIMMUN ELISA®). We employed Bio-Plex Multiplex Cytokine Assay (Bio-Rad Laboratories, Hercules, CA), per manufacturer's instructions, to dose the following cytokines: interleukin (IL)-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, tumor necrosis factor α (TNF- α), interferon- γ (IFN- γ), granulocyte-monocyte colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage

inflammatory proteins (MIP-1 α), and monocyte chemotactic protein-1 (MCP-1). Concentration of analytes were calculated according to a standard curve and expressed as pg/mL. When the concentration of the analytes were below the detection threshold, they were assumed to be 0 pg/mL.

EEG registration and evaluation

Twenty minutes video-EEG recordings were performed, within 2 weeks from lumbar puncture, using a Galileo NT clinical EEG System with 16 electrodes placed according to the International 10–20 system, with a band pass filter of 0.53–50 Hz.

The EEGs were visually assessed and independently scored by two different clinical neurophysiologists (AC and FI), who classified the recordings in categories labelled from 1 to 4, according to ascending values of background rhythm: 7–8 Hz (1), 8–9 Hz (2), 9–10 Hz (3), and 10–11 Hz (4). The first two categories were considered to correspond to slow background activity, while the last two to a faster and more physiologic one. The EEGs were also binomially categorized according to the presence (1) or absence (0) of epileptiform activity, defined as the observation of IEDs on the recording. IEDs were identified as abnormalities having at least 4 out of the 6 criteria established by the International Federation of Clinical Neurophysiology.¹⁴

Statistical analysis

All continuous variables were checked for normality with a Shapiro-Wilk test. As not normally distributed, they were expressed as medians and interquartile ranges. We excluded from the analysis cytokines with more than 5% of values below the limit of detection.

We stratified the population in patients with MCI and patients with early AD dementia, and compared demographic variables (age, sex), AD core biomarkers (CSF $A\beta_{42}$, t-tau, p-tau, p-tau/ $A\beta_{42}$), and CSF cytokines' levels with χ^2 test and Wilcoxon-Mann-Whitney test.

We performed ordered logistic regression analyses on the whole population to predict the association between CSF cytokines levels and EEG background activity, considering it as an ordinal dependent variable. Logistic regressions were used to determine the associations between CSF cytokines levels and the presence of IEDs, the latter considered as a binomial dependent variable. All regression models included the p-tau/ $A\beta_{42}$ ratio, marker of AD pathology burden, as a covariate. Values of $p < 0.05$, adjusted for multiple comparisons, were considered statistically significant. All statistical analyses were performed Stata-Corp® (Stata Statistical Software: Release 13. College Station, TX: StataCorp).

Table 1. Demographic variables, CSF AD biomarkers and cytokines levels, and EEG parameters.

	Study cohort (n = 55)	MCI patients (n = 27)	Early dementia patients (n = 28)	p
Age (y)	73.0 (68.50–75.00)	73.0 (68.0–75.5)	72.5 (69.0–75.0)	0.820
Sex (M:F) (n)	19:36	12:15	7:21	0.130
MMSE	23.9 (22.5–25.3)	25.35 (24.7–26.6)	22.50 (22.0–23.0)	<0.001
CSF A β_{42} (pg/mL)	372.0 (305.0–449.0)	372.0 (320.0–439.5)	379.0 (275.8–457.3)	0.464
CSF p-tau (pg/mL)	63.0 (39.0–85.5)	53.0 (37.0–85.0)	69.0 (46.3–85.3)	0.561
CSF t-tau (pg/mL)	379.0 (220.0–673.0)	341.0 (214.5–631.5)	389.0 (272.8–722.8)	0.619
CSF p-tau/A β_{42}	0.17 (0.12–0.26)	0.15 (0.10–0.18)	0.20 (0.15–0.26)	0.089
CSF IL-1 β (pg/mL)	0.05 (0.005–0.105)	0.06 (0.04–0.11)	0.02 (0.00–0.80)	0.166
CSF IL-2 (pg/mL)	0.00 (0.00–0.25)	0.00 (0.06–0.28)	0.00 (0.00–0.18)	0.780
CSF IL-4 (pg/mL)	0.22 (0.09–0.33)	0.19 (0.56–0.30)	0.24 (0.12–0.33)	0.349
CSF IL-5 (pg/mL)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	n/a
CSF IL-6 (pg/mL)	3.47 (2.20–6.53)	2.66 (2.05–5.72)	3.96 (2.72–6.95)	0.155
CSF IL-7 (pg/mL)	8.39 (3.50–12.36)	8.92 (2.95–12.14)	8.25 (4.02–12.43)	0.743
CSF IL-8 (pg/mL)	20.84 (16.78–24.87)	19.83 (16.94–24.44)	21.25 (16.85–25.20)	0.395
CSF IL-10 (pg/mL)	2.75 (2.48–3.21)	2.71 (2.42–3.01)	2.77 (2.51–3.33)	0.390
CSF IL-12 (pg/mL)	0.60 (0.00–1.82)	0.67 (0.00–1.45)	0.54 (0.00–1.92)	0.932
CSF IL-13 (pg/mL)	0.93 (0.11–1.96)	0.88 (0.00–2.22)	0.93 (0.48–1.72)	0.503
CSF IL-17 (pg/mL)	0.33 (0.00–1.90)	0.00 (0.00–1.86)	0.56 (0.00–1.90)	0.637
G-CSF (pg/mL)	4.78 (3.34–8.03)	5.02 (3.17–8.03)	4.58 (3.40–7.85)	1.000
GM-CSF (pg/mL)	50.97 (34.96–72.71)	50.83 (34.96–73.80)	53.01 (36.21–71.45)	0.946
CSF IFN- γ (pg/mL)	0.00 (0.00–1.67)	0.00 (0.00–1.80)	0.00 (0.00–1.67)	0.873
CSF MCP-1 (pg/mL)	273.29 (2.98–327.79)	232.14 (1.740–292.96)	300.19 (202.17–345.76)	0.028
CSF MIP-1 β (pg/mL)	13.65 (10.91–223.30)	16.93 (12.56–269.86)	12.97 (10.28–19.13)	0.083
CSF TNF- α (pg/mL)	1.09 (0.00–6.27)	2.81 (0.00–7.79)	0.72 (0.00–2.34)	0.214
EEG background rhythm (1:2:3:4) (n)	3:14:22:16	1:8:9:9	2:6:13:7	0.570
EEG IEDs (0:1) (n)	44:11	23:4	21:7	0.345

y: years old; n: numbers; M: male; F: female; MMSE: Mini-Mental State Examination; MCI: mild cognitive impairment; CSF: cerebrospinal fluid; A β_{42} : amyloid- β_{42} ; p-tau: phosphorylated tau; t-tau: total tau; IL: interleukin; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte-monocyte colony stimulating factor; IFN- γ : interferon- γ ; MCP-1: monocyte chemoattracting protein; MIP-1: macrophage inflammatory protein; TNF- α : tumor necrosis factor- α ; EEG: electroencephalogram; IEDs: interictal epileptiform discharges.

Results

The study included 55 patients belonging to the biologically defined AD continuum upon CSF examination (A + T- $n = 26$; A + T + $n = 29$). Clinical and demographical characteristics as well as cytokines and AD biomarkers levels are reported in Table 1.

Comparative analyses between patients with MCI (MMSE ≥ 24 $n = 27$) and patients with early AD dementia (MMSE ≥ 22 and <24 $n = 28$) did not show any significant differences (p -value >0.05) in demographic variables (age, sex), in AD pathology biomarkers (CSF A β_{42} , t-tau, p-tau, p-tau/A β_{42}), nor in levels of CSF inflammatory cytokines, excepting MCP-1 ($p = 0.028$) (see Table 1).

For the regression analyses the data of the two groups were pooled together. The ordered logistic regression analyses showed a significant positive association of EEG background activity with IL-4 CSF levels (coef = 3.347, $p = 0.014$, 95% CI [0.689–6.005]), but not with any other cytokine (all $p > 0.05$) (see Table 2), thus faster background rhythms were associated with higher IL-4 levels. Of note, EEG background activity was not associated with the p-tau/A β_{42} ratio in any of the models.

On the other hand, the logistic regressions showed a significant positive association between the presence of IEDs

and CSF levels of IL-7 (OR = 0.100, $p = 0.045$, 95% CI [0.002–0.198]), IL-8 (OR = 0.070, $p = 0.042$, 95% CI [0.002–0.138]) and IL-12 (OR = 0.729, $p = 0.040$, 95% CI [0.032–1.427]). No association was found with any other cytokine (all $p > 0.05$), nor with the p-tau/A β_{42} ratio.

Discussion

Neuroinflammation and epileptogenic processes are closely intertwined in the cascade of events that leads to A β deposition and neurodegeneration. Subclinical cortical epileptiform activity, defined by the presence of IEDs, has been associated with a temporary increase in functional connectivity, which initially aims to compensate for A β -related excitotoxicity, while promoting plaque formation in the later stages.¹⁵ Albeit being highly prevalent in AD, IEDs are not detected in all patients,¹⁶ implying that amyloid deposition alone may not be sufficient to produce epileptiform activity. We therefore aimed at investigating which factors could precipitate the epileptogenic potential of A β oligomers, hypothesizing a predominant role for central neuroinflammation. The recent demonstration of functional interactions between cytokines and classical neurotransmitters such as glutamate and GABA, suggest the possibility

Table 2. Results from ordered logistic and logistic regression analyses adjusted by p-tau/A β_{42} .

Variable	EEG background activity		IEDs	
	Coef.	p	OR	p
IL-1 β	-0.899	0.619	-2.05	0.624
IL-2	1.313	0.174	1.697	0.150
IL-4	3.347	0.014*	2.559	0.124
IL-6	0.060	0.107	0.042	0.359
IL-7	0.080	0.087	0.100	0.045*
IL-8	0.038	0.156	0.070	0.042*
IL-10	0.240	0.537	-0.745	0.237
IL-12	0.442	0.084	0.729	0.040*
IL-13	0.125	0.471	0.405	0.083
IL-17	0.087	0.625	0.023	0.923
G-CSF	0.113	0.109	0.145	0.107
GM-CSF	0.016	0.088	-0.001	0.889
IFN- γ	0.072	0.705	0.070	0.783
MCP-1	-0.0005	0.756	0.000	0.091
MIP-1 β	0.001	0.436	-0.001	0.908
TNF- α	0.072	0.259	-0.032	0.719

Bold values represent statistical significance (*p < 0.05).

IEDs: interictal epileptiform discharges; OR: odds ratio; IL: interleukin;

G-CSF: Granulocyte colony stimulating factor; GM-CSF:

granulocyte-monocyte colony stimulating factor; IFN- γ : interferon- γ ;

MCP-1: monocyte chemoattracting protein; MIP-1: macrophage

inflammatory protein; TNF- α : tumor necrosis factor- α .

that these interactions underlie the cytokine-mediated changes in neuronal excitability, thus promoting IEDs occurrence.¹⁷

Indeed, compelling evidence points towards a dualistic effect of inflammation, both beneficial and detrimental, possibly mediated by different microglial activation modalities and different permeability states of the blood-brain barrier.¹⁸ In the initial stages of neurodegeneration, characterized by synapse dysfunction and neuronal loss, a damage-repair response may be triggered, leading to the release of neurotrophic and proangiogenic factors.¹⁹ On the other hand, aberrant neuroinflammation can exacerbate amyloid deposition and neuronal loss, further disrupting synaptic plasticity and leading to AD-associated epileptic changes.²⁰

In our sample, AD core biomarkers (CSF A β_{42} , t-tau, p-tau, p-tau/A β_{42}) were not significantly different among patients with MCI and patients with early dementia. This supports the hypothesis that AD pathology exists along a continuum, independent of clinical stage.¹¹ Furthermore, there were no differences in CSF cytokines levels except for MCP-1, whose role in AD pathogenesis is not supported by solid evidence in literature.²¹ A possible explanation for our findings could be that the subjects with dementia were in an early stage, bearing pathological changes similar to those of the MCI patients, while more pronounced differences could be detected at more advanced stages.

As such, we considered the population as a whole when investigating the association of inflammation and cortical

activity changes. In line with the potential beneficial role of neuroinflammation in AD pathology, our findings revealed that higher CSF levels of IL-4 were associated with faster EEG background activity. At a central level, this cytokine promotes microglial clearance of A β oligomers²² and supports the synaptic pruning and function via the IL-4 receptor- α located directly on neurons.²³

Conversely, higher levels of CSF IL-7 and IL-12, expression of a pro-inflammatory milieu,^{24,25} were associated with the presence of IEDs. IL-7 has been linked with the activation of proapoptotic pathways in neurons and increased levels have been found in the blood of drug-resistant epileptic patients.²⁶ As for IL-12, in an animal model of aging brain, inhibiting the IL-12/IL-23 signaling has been associated with decreased A β levels and reduced synaptic loss,²⁷ suggesting a role for this cytokine in AD-related cortical dysfunction. Furthermore, we found a positive association between IEDs and CSF levels of IL-8. This cytokine has long been considered neuroprotective, but recent studies revealed that IL-8 CSF levels may rise in early AD stages²⁰ and in the CSF of patients with pharmacoresistant epilepsy.^{28,29}

Overall, our findings suggest that, in patients with AD pathology the presence of a damage-repairing inflammatory response (i.e., higher IL-4 CSF levels) is associated with a physiological EEG activity, reflected by higher background activity frequencies. Concurrently, a pro-inflammatory pattern (i.e., IL-7, IL-8, and IL-12 CSF levels), likely developed in response to neurodegenerative processes, is associated with the presence of epileptiform abnormalities. Of note, several studies suggest other crucial pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 to be overexpressed in experimental seizure models,³⁰ but we did not find any association between these cytokines and any EEG abnormality in our cohort. The lack of association with these cytokines could stem from our focus on interictal rather than ictal abnormalities, as well as from the selection of patients with biologically defined AD pathology.

A limitation of our study is the small sample size and lack of a control cohort, that limited the statistical approach. Moreover, the cross-sectional design did not allow to evaluate the eventual impact of these EEG changes on cognitive decline. However, to our knowledge, this is the first investigation on the association between CSF cytokines levels and EEG abnormalities in AD patients, and our findings underscore the importance of considering neuroinflammatory markers when investigating the relationship between cortical dysfunction and AD pathological hallmarks.

In conclusion, while neuroinflammation may act as a beneficial factor to counterbalance the damages due to neurodegeneration it may also favor amyloid's epileptogenic potential, leading to possible deleterious effects on cognition and to an accelerated disease course.³¹ Understanding the interplay between neuroinflammation and epileptiform abnormalities in AD patients would be crucial for

developing targeted therapeutic interventions aimed at differently modulating these inflammatory processes and reducing hyperexcitability and epileptiform activity in selected patients.

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Statements and declarations

Author contributions

Matilde Bruno (Data curation; Writing – original draft); Chiara Giuseppina Bonomi (Formal analysis; Methodology; Writing – review & editing); Alessandro Castelli (Data curation; Methodology); Francesca Izzi (Conceptualization; Supervision; Writing – review & editing); Fabio Placidi (Funding acquisition; Supervision; Validation); Silvia Falletti (Investigation; Visualization); Nicola Biagio Mercuri (Supervision; Validation); Caterina Motta (Conceptualization; Formal analysis; Writing – original draft); Alessandro Martorana (Project administration; Supervision).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Italian Ministry of Health [Research Grant: RF-2018-12365527].

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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