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PHENOBARBITAL-INDUCED CD4+ UP-REGULATION PREDICTS SEIZURE REDUCTION IN EPILEPSY

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In this prospective pilot cohort study (November–December 2024, Kadhimiya Hospital, Iraq), 40 patients (26 men, 14 women; ages 25-50) with confirmed epilepsy received oral phenobarbital (10 mg/mL, 12 weeks). CD4+ concentrations (ng/mL via ELISA after MACS isolation) and seizure frequency were assessed pre- and post-treatment. Paired t-tests, ANOVA, and Pearson correlations were used ($p<0.05$ significant; effect sizes reported). CD4+ levels increased from 15,2 ± 4,3 ng/mL to 22,8 ± 5,6 ng/mL ($p<0,001$; Cohen's d=1,35; 95% CI for difference: 5,9-9,3). Seizure frequency decreased by 78% (8,9 ± 3,79 to 1,93 ± 1,53; $p<0,001$; Cohen's d=2,01). Post-treatment CD4+ inversely correlated with seizure frequency ($r=-0,62$, $p<0,001$; 95% CI: -0,78 to -0,40) and positively with clinical response ($r=0,85$, $p<0,001$; 95% CI: 0,75 to 0,91). Patients with CD4+ >22 ng/mL had 83% response rate versus 42% below. Females showed higher response rates (80% versus 73% males) despite lower CD4+ folds. Thus, PB is associated with CD4+ upregulation and seizure reduction, suggesting potential as a biomarker of therapeutic response.

Key words: *epilepsy, phenobarbital, CD4+ lymphocytes, immunomodulation, biomarkers*

Introduction

Epilepsy, a chronic neurological disorder characterized by recurrent unprovoked seizures, affects approximately 50 million people worldwide, with significant morbidity and socioeconomic burden, particularly in resource-limited settings [1]. The cornerstone of management remains antiseizure medications (ASMs), which suppress neuronal hyperexcitability. Phenobarbital (PB), a barbiturate used for over a century, is a first-line ASM in low- and middle-income countries due to its affordability and efficacy [2]. Its primary mechanism involves enhancing GABA-mediated inhibition via GABAA receptor modulation [3]. However, emerging evidence suggests PB also modulates neuroimmune interactions, which are increasingly recognized in epileptogenesis [4].

Neuroinflammation, including microglial activation and immune cell infiltration, is prominent in drug-resistant epilepsy (DRE). CD4+ T lymphocytes, key adaptive immunity regulators, are implicated: DRE patients show elevated proinflammatory Th1/Th17 subsets, releasing cytokines (e.g., IL-17A, TNF-α, IFN-γ) that promote blood-brain barrier disruption and neuronal injury [5]. Conversely, regulatory T cells (Tregs) may mitigate inflammation and seizures in preclinical models [6].

ASMs like PB influence immune parameters, reducing lymphocyte cytotoxicity and CD4+/CD8+ ratios [7]. PB shows milder immunosuppression than other barbiturates and inhibits microglial activation in models [8]. Yet, clinical data linking PB-induced CD4+ changes to seizure outcomes are scarce.

This prospective pilot study hypothesized that PB upregulates CD4+ lymphocytes in patients with epilepsy, correlating with reduced seizure frequency.

Methods

Study Design and Participants

This prospective pilot cohort study was conducted at the Neurology Department, Kadhimiya Hospital, Baghdad, Iraq (October-December 2024).

Forty patients with epilepsy (26 men, 14 women; ages 25-50) were enrolled. Diagnosis followed ILAE guidelines [1].

Inclusion: Confirmed epilepsy (focal/generalized), age 25-50, treatment-naïve or stable ASM for ≥6 months, informed consent.

Exclusion: Immunomodulatory therapies, autoimmune disorders, significant comorbidities, pregnancy/lactation, PB hypersensitivity.

Sample size was powered (80% power, effect size 0,5, alpha 0,05) for CD4+ differences, targeting 34; 40 enrolled for dropouts.

Intervention

Patients received phenobarbital (PB) at a standardized dose of 10 mg/mL, administered orally as part of their treatment regimen. The treatment duration was 12 weeks, with PB administered daily at a dose adjusted to achieve therapeutic plasma levels (15-40 μg/mL), monitored via regular blood tests.

Compliance was assessed through patient diaries and pill counts, with adherence rates >90% required for inclusion in the final analysis. Pre-treatment baseline assessments were conducted within 1 week prior to initiating PB, and post-treatment assessments were performed within 1 week after completing the 12-week treatment period.

Data Collection

Peripheral blood samples (5 mL) were collected from each participant at baseline (pre-treatment) and post-treatment using sterile venipuncture techniques into EDTA-coated tubes. Samples were processed within 2 hours of collection to ensure cell viability. CD4+ T-cells were isolated from peripheral blood mononuclear cells (PBMCs) using a magnetic-activated cell sorting (MACS) system (Miltenyi Biotec, Germany), following the manufacturer's protocol.

CD4+ lymphocyte concentrations were quantified in ng/mL using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (e.g., Human CD4 ELISA Kit, Abcam, catalog number ab133616), with a sensitivity of 0,1 ng/mL and intra- and inter-assay coefficients of variation <10%.

The ELISA procedure was performed in duplicate for each sample, and mean values were used for analysis. Calibration curves were generated using standard controls provided in the kit, ensuring linearity across the measurement range (0,1-100 ng/mL).

Seizure frequency was recorded via standardized patient diaries, cross-verified through clinical interviews at baseline and post-treatment visits. Seizure frequency was expressed as the number of seizures per month, with baseline frequency calculated over the 3 months prior to enrollment and post-treatment frequency calculated over the final 4 weeks of treatment.

Epilepsy type (focal or generalized) was classified based on EEG findings and clinical presentation, adhering to ILAE criteria.

Demographic and clinical data, including age, sex, epilepsy duration, and prior ASM use, were collected via structured questionnaires and medical record reviews.

Statistical Analysis

Data were analyzed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Continuous variables (e.g., CD4+ levels, seizure frequency) were expressed as mean ± standard deviation (SD), and categorical variables (e.g., response categories, epilepsy type) were expressed as frequencies and percentages. Normality of data distribution was assessed using the Shapiro-Wilk test, confirming that CD4+ levels and seizure frequency data were normally distributed ($p > 0,05$).

Paired t-tests were used to compare pre- and post-treatment CD4+ levels and seizure frequencies within the cohort. Independent t-tests examined differences in CD4+ induction and response rates between gender groups (male/female). One-way analysis of variance (ANOVA) assessed differences in CD4+ levels across epilepsy types (focal/generalized), followed by post hoc Bonferroni tests for pairwise comparisons to control for multiple comparisons.

Pearson correlation coefficients were calculated to evaluate relationships between:

– post-treatment CD4+ levels and seizure frequency, and

– CD4+ induction (fold change) and treatment response.

Clinical response was categorized as «no response» (no reduction in seizure frequency), «partial response» (<50% reduction in seizure frequency), or «full response» (≥50% reduction in seizure frequency), based on established epilepsy research criteria. A two-tailed p-value < 0,05 was considered statistically significant for all analyses. Effect sizes were reported where applicable (e.g., Cohen's d for t-tests, eta-squared for ANOVA) to quantify the magnitude of observed differences.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of Kadhimiya Hospital, and all procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment, with consent forms available in Arabic and English to ensure comprehension. Participants were informed of their right to withdraw from the study at any time without penalty. Confidentiality was maintained by assigning unique study identifiers to all data, with personal information stored in a secure, password-protected database accessible only to the research team. No adverse immune events (e.g., hyperinflammatory responses, infections) were reported during the study, and CD4+ levels remained within physiologic limits (<50 ng/mL), minimizing risks to participants. Safety monitoring included regular clinical assessments and blood tests to detect potential PB-related adverse effects (e.g., hepatotoxicity, hematologic abnormalities).

Results

Forty patients with epilepsy were enrolled and analyzed (no dropouts). Baseline characteristics included a mean age of 37,5±8,2 years (95% CI: 34,9-40,1), with 26 (65%) men and 14 (35%) women. Epilepsy types were focal in 28 (70%) and generalized in 12 (30%), with a mean duration of 8,3±4,1 years (95% CI: 7,1-9,5). Thirty-two patients (80%) were on stable prior antiseizure medications. Baseline seizure frequency was 8,9±3,79 seizures per month (95% CI: 7,7-10,1), and baseline CD4+ concentrations were 15,2±4,3 ng/mL (95% CI: 13,8-16,6; table 1).

Table 1 – Baseline characteristics of study participants (N = 40)

Characteristic	Value
Age, years (mean ± SD; 95% CI)	37,5 ± 8,2 (34,9-40,1)
Sex, n (%)	
Male	26 (65%)
Female	14 (35%)
Epilepsy type, n (%)	
Focal	28 (70%)
Generalized	12 (30%)
Epilepsy duration, years (mean ± SD; 95% CI)	8,3 ± 4,1 (7,1-9,5)
Prior ASM use, n (%)	32 (80%)
Baseline seizure frequency, seizures/month (mean ± SD; 95% CI)	8,9 ± 3,79 (7,7-10,1)
Baseline CD4+ concentrations, ng/mL (mean ± SD; 95% CI)	15,2 ± 4,3 (13,8-16,6)

Table 2 – CD4+ concentrations (ng/mL) before and after PB treatment (N=40)

Group	Mean ± SD (95% CI)	Range	p-value	Effect Size (Cohen's d)
Pre-treatment	15,2 ± 4,3 (13,8-16,6)	7,9-23,0	<0,001	1,35
Post-treatment	22,8 ± 5,6 (21,0-24,6)	15,9-37,5		

Phenobarbital treatment significantly increased CD4+ lymphocyte levels in epileptic patients. The mean CD4+ concentration rise from 15,2±4,3 ng/mL pre-treatment to 22,8±5,6 ng/mL post-treatment, representing a 49,7% increase (Δ = +7,6 ng/mL, paired t-test, t(39) = 8,54, p <0,001, Cohen's d = 1,35; table 2).

The post-treatment distribution showed greater variability (range: 15,9–37,5 ng/mL) compared to pre-treatment (range: 7,9–23,0 ng/mL), indicating inter-individual differences in immunologic responsiveness.

Seizure frequency decreased markedly post-treatment, from 8,9±3,79 seizures per month to 1,93±1,53, representing a 78% reduction (paired t-test, t(39) = 12,67, p <0,001, Cohen's d = 2,01). Clinical response was categorized as follows: 25 patients (62,5%) achieved «full» response (≥50% seizure reduction), 5

(12,5%) had «partial» response (<50% reduction), and 10 (25%) showed «no» response (no reduction in seizure frequency; table 3).

The proportion of patients with «no» response decreased from 100% pre-treatment (by definition, as all had active seizures) to 25% post-treatment, while 75% achieved at least partial response.

An inverse correlation was observed between post-treatment CD4+ concentrations and seizure frequency (Pearson r=-0,62, p<0,001, 95% CI: -0,78 to -0,40). A positive correlation existed between CD4+ fold change (post/pre ratio) and treatment response (r=0,85, p<0,001, 95% CI: 0,75–0,91; table 4).

Patients with post-treatment CD4+ >22 ng/mL had an 83% response rate (full or partial) compared to 42% for those ≤22 ng/mL.

In subgroup analyses, patients with focal epilepsy had slightly higher mean fold changes in CD4+ levels (2,9 ± 1,2) compared to those with generalized epilepsy (2,6 ± 0,9), but the difference was not statistically significant (independent t-test, t(38) = 0,78, p = 0,44, Cohen's d = 0,28; table 5).

Gender differences were notable. Females had lower fold increases in CD4+ levels (2,4±0.8) compared to males (2,8±1,1), though this difference was not statistically significant (independent t-test, t(38) = 1,23, p = 0,23, Cohen's d = 0,40). However, females demonstrated higher response rates (80%, 11/14) compared to males (73%, 19/26; table 6).

Significant differences in post-treatment CD4+ levels were observed across response categories (one-way ANOVA, F(2,37) = 12,34, p < 0,001, eta-squared = 0,40). Post hoc Bonferroni tests revealed that the «no response» group had significantly lower CD4+ levels (17,09±5,3 ng/mL) compared to the «partial» (24,38±7,0 ng/mL, p = 0,016) and «full» response groups (22,38±5,3 ng/mL, p < 0,001), with no significant difference between partial and full responders (p = 1,0; table 7).

This prospective pilot study demonstrates an association between phenobarbital (PB) treatment and significant upregulation of CD4+ lymphocyte concentrations (49,7% increase, from 15,2±4,3 ng/mL to

Table 3 – Clinical response pre- and post-treatment

Characteristics	Pre-treatment N (%)	Post-treatment N (%)
No	40 (100%)	10 (25%)
Partial	0	5 (12,5%)
Full	0	25 (62,5%)
Seizures, seizures/month (mean ± SD; 95% CI)	8,9 ± 3,79 (7,7-10,1)	1,93 ± 1,53 (1,4-2,4)
CD4+ concentrations, ng/mL (mean ± SD; 95% CI)	15,2 ± 4,3 (13,8-6,6)	22,8 ± 5,6 (21,0-24,6)

Table 4 – Correlations involving CD4+ concentrations

Comparison	Pearson r (95% CI)	p-value
CD4+ versus Seizure Frequency	-0,62 (-0,78 to -0,40)	<0,001
CD4+ Fold Change versus Response	0,85 (0,75 to 0,91)	<0,001

Table 5 – CD4+ Fold Change by Epilepsy Type

Epilepsy Type	N	Mean Fold Change ± SD (95% CI)	p-value	Effect Size (Cohen's d)
Focal	28	2,9 ± 1,2 (2,4-3,4)	0,44	0,28
Generalized	12	2,6 ± 0,9 (2,0-3,2)		

Table 6 – Response by CD4+ Fold Change in Subgroups

Subgroup	N	Mean Fold Change ± SD (95% CI)	Responders, n (%)
Epilepsy Type			
Generalized	12	2,6 ± 0,9 (2,0-3,2)	9 (75%)
Focal	28	2,9 ± 1,2 (2,4-3,4)	21 (75%)
Gender			
Female	14	2,4 ± 0,8 (1,9-2,9)	11 (80%)
Male	26	2,8 ± 1,1 (2,4-3,2)	19 (73%)

Table 7 – CD4+ Levels (ng/mL) by Response Type

Response	N	Mean ± SD (95% CI)	p-value (ANOVA)	Effect Size (eta-squared)
No	10	17,09 ± 5,3 (13,1-21,1)	<0,001	0,40
Partial	5	24,38 ± 7,0 (15,9-32,9)		
Full	25	22,38 ± 5,3 (20,4-24,4)		

Note: Post hoc Bonferroni: «No» vs. «Partial» p=0,016; «No» vs. «Full» p<0,001; «Partial» vs. «Full» p=1,0.

22,8±5,6 ng/mL; p<0.001) in patients with epilepsy, alongside a marked reduction in seizure frequency (78%, from 8,9±3,79 to 1,93±1,53 seizures per month; p<0.001).

The inverse correlation between post-treatment CD4+ levels and seizure frequency (r=-0,62, p<0,001; 95% CI: -0,78 to -0,40) and the positive correlation with clinical response (r=0,85, p<0,001; 95% CI: 0,75 to 0,91) suggest that CD4+ modulation may be linked to therapeutic outcomes.

Patients achieving CD4+ levels >22 ng/mL post-treatment experienced an 83% response rate (full or partial) compared to 42% below this threshold, highlighting potential biomarker utility. Subgroup trends, such as higher response rates in females (80% versus 73% in males) despite lower CD4+ fold changes, and slightly greater induction in focal epilepsy (2.9x versus 2.6x in generalized; p=0.44), provide preliminary insights into demographic and phenotypic influences.

These findings align with emerging evidence on neuroimmune interactions in epilepsy, where CD4+ T-cells contribute to both epileptogenesis and resolution [9]. For instance, recent studies have shown elevated proinflammatory CD4+ subsets (e.g., Th1/Th17) in drug-resistant epilepsy, correlating with neuronal injury markers like neurofilament light chain [10]. Our observed CD4+ upregulation complements preclinical reports of immune modulation reducing seizure severity, such as through regulatory T-cell (Treg) expansion that dampens cytokine-driven inflammation [11]. The strong correlations in our cohort echo human data linking peripheral T-cell profiles to seizure activity, as in medial temporal lobe epilepsy where CD4+ numbers correlate with neuronal loss. However, our results contrast with some ASM studies reporting immunosuppressive effects (e.g., reduced CD4+/CD8+ ratios) [12], suggesting PB's impact may be context-dependent, potentially favoring protective immune responses in epilepsy.

The mechanisms underlying the observed associations remain speculative but may involve multiple pathways. PB, traditionally known for GABA_A receptor potentiation, could indirectly influence CD4+ levels by reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6), shifting T-helper balances toward anti-inflammatory Tregs [13]. This is supported by preclinical evidence of PB inhibiting microglial activation and cytokine release in epilepsy models [14]. Additionally, PB may stabilize the blood-brain barrier (BBB), limiting pathogenic CD4+ infiltration into epileptic foci while elevating peripheral levels as a marker of restored homeostasis. GABAergic signaling on immune cells offers another plausible link, as GABA receptors on T-cells modulate proliferation and cytokine production. These pathways could explain how CD4+ induction correlates with seizure control, potentially reflecting reduced neuroinflammation and neuronal hyperexcitability. Gender differences, with females showing better outcomes, may relate to estrogen's enhancement of T-cell responses, consistent with 2022 immunology reviews [15]. Similarly, trends in focal epilepsy align with localized immune activation in lesions.

These preliminary findings have implications for epilepsy management, particularly in resource-limited settings where PB is widely used. CD4+ profiling could serve as a hypothesis-generating biomarker for response prediction, enabling personalized strategies like dose adjustments or adjunctive therapies in DRE.

Conclusion

This prospective pilot study associates phenobarbital treatment (10 mg/mL) with a

49,7% increase in CD4+ lymphocyte concentrations and a 78% reduction in seizure frequency among 40 patients with epilepsy. The inverse correlation between post-treatment CD4+ levels and seizure frequency (r=-0,62, p<0,001) and positive correlation with clinical response (r=0,85, p<0,001), along with an 83% response rate for CD4+ >22 ng/mL versus 42% below, suggest CD4+ as a potential biomarker for therapeutic efficacy. No adverse immune events occurred, with CD4+ levels remaining within physiologic limits (<50 ng/mL), supporting PB's safety profile in this cohort.

These findings extend PB's role beyond GABAergic mechanisms to potential neuroimmune modulation, offering insights for epilepsy management in resource-limited settings.

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ФЕНОБАРБИТАЛ-ИНДУЦИРОВАННОЕ ПОВЫШЕНИЕ УРОВНЯ CD4+-ЛИМФОЦИТОВ ПРЕДСКАЗЫВАЕТ СНИЖЕНИЕ ЧАСТОТЫ ПРИСТУПОВ ПРИ ЭПИЛЕПСИИ

В настоящем проспективном пилотном когортном исследовании (ноябрь – декабрь 2024 года, больница Аль-Кадимия, Ирак) исследовано 40 пациентов (26 мужчин и 14 женщин) в возрасте от 25 до 50 лет с подтверждённым диагнозом эпилепсии, которым орально назначали фенобарбитал (ФБ) в дозе 10 мг/мл в течение 12 недель. Концентрации CD4+ (нг/мл) определялись методом ELISA после изоляции с помощью MACS), частота приступов оценивалась до и после лечения. Для статистической обработки исполь-

зовались парные t-критерий, диперсионный и корреляционный анализ (коэфициент корреляции Пирсона, $p < 0,05$ считалось статистически значимым; также указывались размеры эффекта). Уровни CD4+ увеличились с 15,2±4,3 нг/мл до 22,8±5,6 нг/мл ($p <0,001$; коэффициент Коэна $d = 1,35$; 95% доверительный интервал разницы: 5,9–9,3). Частота приступов снизилась на 78% (с 8,9±3,79 до 1,93±1,53; $p < 0,001$; $d = 2,01$). После лечения уровень CD4+ отрицательно коррелировал с частотой приступов ($r = –0,62$, $p <0,001$; 95% ДИ: от -0,78 до -0,40) и положительно – с клиническим ответом ($r = 0,85$, $p <0,001$; 95% ДИ: 0,75–0,91). У пациентов с уровнем CD4+ выше 22 нг/мл наблюдалась частота ответа 83%, тогда как у пациентов с более низким уровнем – только 42%. Для женщин показана более высокая частота ответа (80%) по сравнению с мужчинами (73%), несмотря на меньший прирост CD4+. Таким образом, фенобарбитал связан с повышением уровня CD4+ и снижением частоты эпилептических приступов, что указывает на его потенциал в качестве биомаркера терапевтического ответа.

Ключевые слова: *эпилепсия, фенобарбитал, CD4+-лимфоциты, иммуномодуляция, биомаркеры*

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