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Research Article

Adipokine and cytokine profiles in pediatric epilepsy: a comparative analysis of epilepsy level of control and drug resistance

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Abstract

The role of adipokines and inflammatory cytokines in the pathogenesis of epilepsy has been inconsistently described in the literature. Hence, the presence of distinguishing serum inflammatory markers for epilepsy, controlled epilepsy (CE), and uncontrolled epilepsy (UCE), including drug-resistant epilepsy (DRE) and non-drug-resistant epilepsy (NDRE), remains unclear. Therefore, the aim of this cross-sectional study was to characterize the serum levels of leptin, adiponectin, resistin, and an extended panel of inflammatory cytokines among the aforementioned groups of pediatric patients and in comparison with healthy controls (HCs).

The study demonstrated that leptin and adiponectin levels were significantly higher in pediatric patients with epilepsy than in HCs, while resistin levels were significantly lower. The levels of adiponectin and resistin, but not leptin, were significantly higher in DRE than in CE. Tumor necrosis factor-α (TNF-α) levels were significantly higher in the DRE group than in the uncontrolled NDRE or CE groups. Binary logistic regression analysis showed that only resistin and TNF-α had significant predictive value for DRE compared with other epilepsy patients. Multiple linear regression analysis demonstrated that mannose-binding lectin (MBL), resistin, and body mass index (BMI) were the strongest predictors of leptin levels in pediatric epilepsy. Leptin levels, a shorter duration of time since the last seizure, and age were the strongest predictors of higher resistin levels. The presence of developmental delay and lower patient weight predicted higher adiponectin levels.

These findings may aid in distinguishing patients with DRE, NDRE, and CE. Resistin and TNF-α might be potential new targets for disease-modifying, anti-inflammatory therapy in pediatric epilepsy, particularly for DRE.

Keywords

adipokines, children, drug-resistant, inflammatory cytokines, pediatric, refractory epilepsy

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PENSOFT

Introduction

Epilepsy definition and epidemiology

Epilepsy is considered the fourth most common neurological disorder in the world (Hollis and Lukens 2025). This chronic brain condition is characterized by the experience of two or more unprovoked seizures more than 24 h apart (Fisher et al. 2014). The prevalence of childhood epilepsy at ages of 5–9 years is 374.8 cases (95% CI: 280.1–490.0) per 100,000 population. The incidence of childhood epilepsy varies from 41 to 187 cases per 100,000 population, with higher incidences observed in lower-middle-income countries (Menon and Helen Cross 2025).

Epilepsy etiology and pathogenesis

The pathophysiological mechanisms of childhood-onset epilepsy depend on several etiologies, including structural (genetic, acquired, or both), genetic, metabolic, infectious, immune-mediated, or unknown causes (Menon and Cross 2025). Recent studies have demonstrated the involvement of central nervous system (CNS) inflammation and systemic inflammation in the pathogenesis of epilepsy (Toledo et al. 2021; Sokolova et al. 2022; Diler Durgut et al. 2025).

Current treatment approaches and challenges in therapy

Standard anti-seizure medications

Antiseizure medications (ASMs), as monotherapy or combination therapy, are considered the first-line management for children with epilepsy. More than 25 ASMs are available, including older-generation (such as valproate) and newer-generation ASMs (such as lamotrigine) (Menon and Cross 2025). Regimen selection is based on epilepsy subtype, EEG, and clinical features. However, this selection is complicated by several factors, including the wide range of pharmacokinetic and pharmacodynamic properties of ASMs, drug–drug interactions, safety considerations during childhood, and the presence of other comorbidities. Furthermore, the most challenging issue in therapy is the presence of drug resistance, which necessitates alternative therapies (Menon and Cross 2025). Drug-resistant epilepsy (DRE) was defined by the International League Against Epilepsy as the failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (i.e., therapeutic failure of at least two ASMs used at maximum tolerable therapeutic doses to achieve seizure freedom) (Kwan et al. 2010; Téllez-Zenteno et al. 2014).

Alternative treatment approaches

In the case of DRE, standard ASMs fail to achieve seizure control. Therefore, new management modalities, such as ketogenic diet therapy and surgery, are available (Menon and Cross 2025). Ketogenic diet therapy is composed of a high-fat, low-carbohydrate diet that aims to generate ketones. However, response rates to the use of the ketogenic diet as adjunctive therapy in DRE are approximately 30–40% (Martin-McGill et al. 2020; Menon and Cross 2025). Surgical intervention is another option for DRE and other selected cases of epilepsy (Menon and Cross 2025).

Cognitive impact of epilepsy

Outcomes of childhood epilepsy with continuing seizures during adulthood include poor performance on measures of language, semantic skills, and visuomotor skills compared with those with remitted epilepsy or healthy control individuals (Karrasch et al. 2017). In addition, features of autism spectrum disorder have been shown to be more common in children with epilepsy than in healthy controls, regardless of cognitive impairment (Reilly et al. 2015).

The role of adipokines and inflammatory cytokines in the pathogenesis of epilepsy

Adipokines, such as leptin, adiponectin, and resistin, have been suggested to play a role in the inflammatory process in epilepsy, seizure generation, and neuroprotection (Palmio et al. 2016; Shan et al. 2023). In addition to their role in the regulation of energy metabolism, they have immunomodulatory properties affecting both the innate and adaptive immune systems. Leptin and resistin have proinflammatory effects, while adiponectin exerts anti-inflammatory effects (Tilg and Moschen 2006; Shan et al. 2023). Leptin, in particular, has a dual effect in epilepsy, exhibiting both a neuroprotective role and proconvulsant activity in different models of epilepsy (Shan et al. 2023). However, inconsistent results have been reported regarding their levels in patients with epilepsy (Palmio et al. 2016; Toscano et al. 2019; Chen et al. 2020; Shan et al. 2023), and most of these studies were conducted in adults, patients with temporal lobe epilepsy (TLE), or during the acute phase of seizures (within 24 h) (Palmio et al. 2016; Ethemoglu et al. 2018; Toscano et al. 2019; Chen et al. 2020). Therefore, little is known about their levels in children during the post-seizure phase.

Regarding inflammatory cytokines, it has been reported that acute epileptic seizures are associated with elevated levels of proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (Palmio et al. 2016; Alapirtti et al. 2018; Soltani Khaboushan et al. 2022). Outside the acute seizure phase, proinflammatory cytokines—such as IL-1β, TNF-α, or IL-6—have also been documented to play a key role in chronic brain inflammation in epilepsy (Elhady et al. 2022; Hollis and Lukens 2025). However, the results of previous reports on the types and levels of inflammatory mediators altered in epilepsy have been variable (Elhady et al. 2022). Some reports, for instance, have shown a significant increase in systemic serum levels of IL-6 and TNF-α in patients with epilepsy, while others have demonstrated no

significant differences in the serum levels of the aforementioned cytokines or IL-1β compared with healthy controls (Elhady et al. 2022; Milano et al. 2024). Therefore, there is a need to further explore and understand alterations in inflammatory mediators and adipokines in epilepsy, particularly in the pediatric population outside the acute seizure phase. This could provide new therapeutic targets for the management of this chronic disorder, which are urgently needed, considering that one-third of patients with epilepsy are resistant to the available ASMs (Löscher et al. 2020; Perucca et al. 2023). Neuroinflammation in DRE has been suggested to involve CNS infiltration by innate immune cells, such as monocytes and neutrophils, and a neuroinflammatory process involving TNF-α, IL-1β, and IL-6 cytokines (Shi et al. 2025). However, discrepancies in the literature regarding the serum levels of these cytokines in patients with DRE have been reported (Zawadzka et al. 2025). Significant increases in the systemic levels of IL-1, IL-1β, IL-10, IL-5, IL-6, TNF-α, IL-1R1, IL-4, and IL-7 have been observed in patients with DRE (Choi et al. 2020; Toledo et al. 2021; Sokolova et al. 2022; Diler Durgut et al. 2025). On the other hand, several reports have demonstrated either no change or an insignificant increase in the levels of IL-1β, IL-1RA, interferon-γ (IFN-γ), and IL-10 in patients with DRE compared with healthy controls (Choi et al. 2020; Sokolova et al. 2022). Previous studies that investigated the levels of adipokines in DRE have focused mainly on the impact of the ketogenic diet on adipokine levels or were conducted in adults (Ethemoglu et al. 2018; Chyra et al. 2021, 2022). Thus, there is a need to investigate the levels of adipokines and inflammatory mediators in the pediatric population regardless of the specific treatment strategy or ASM used.

A large body of literature has investigated the types and levels of inflammatory cytokines and adipokines in epilepsy. However, the inconsistency of the literature results and the variability of the settings in different studies have made it difficult to establish clear associations between the levels of different cytokines and the epilepsy status of patients. Furthermore, most studies that investigated the levels of inflammatory cytokines and adipokines have focused on adult populations, compared the impact of specific antiseizure treatments on their levels, or explored their levels during the acute phase of seizures (Palmio et al. 2016; Ethemoglu et al. 2018; Toscano et al. 2019; Chen et al. 2020; Chyra et al. 2021, 2022). Therefore, to the best of current knowledge, little is known about the levels of inflammatory cytokines and adipokines in pediatric populations with epilepsy exhibiting variable levels of epilepsy control and drug resistance status, regardless of the ASM used.

Hence, the current report presents a comprehensive comparative analysis of the levels of an extended panel of inflammatory cytokines and adipokines in relation to the control status and drug resistance status of pediatric patients with epilepsy who were seizure-free for at least 72 h and in comparison with healthy controls. The study also aimed to identify inflammatory mediators predictive of DRE and clinical parameters associated with the levels of the analyzed mediators. The results of this report could aid in the identification of cytokines associated with the different control statuses of patients, including the risk of DRE, and could provide new therapeutic targets for the development of disease-modifying agents for the management of epilepsy.

Methods

Study subjects

Pediatric patients with epilepsy aged <18 years who were seizure-free for at least 72 h were included. This time interval was chosen to minimize the impact of acute seizures on cytokine release kinetics. Patients were excluded if they had any other neurological conditions or any condition that might be associated with changes in inflammatory status, including active infection, thyroid dysfunction, chronic inflammatory diseases, autoimmune diseases, cancer, renal impairment, hepatic impairment, surgery or major trauma in the previous month, or use of immunosuppressive or immunomodulatory medications in the 6 weeks prior to the study.

In this cross-sectional study, a minimum reliable target sample size was estimated based on the following equation: $Z_{1-\alpha/2}{}^2 P(1-P)/d^2$, where Z is the standard normal variate = 1.96 at a 5% type I error rate ($p < 0.05$); P is the expected population proportion (1% in the current study, based on the global prevalence of childhood epilepsy (Aaberg et al. 2017)); and d is the absolute error or precision, equal to one-half of the desired confidence interval width (in this study, d = 5%) (Charan and Biswas 2013). The minimum sample size was found to be approximately 15. Previous reports on epilepsy that employed a similar study design used a target sample size of approximately 20 patients for each group (Gakharia et al. 2022; Yaryari et al. 2022). Therefore, a similar target sample size was used for each group; consequently, the target sample size of the whole study population in the current study was approximately 60.

Study protocol

Sixty-seven eligible children with epilepsy who presented to the neurology clinic at the University of Jordan Hospital between June 2020 and June 2022 were enrolled. Patients were divided into two main groups based on epilepsy control status. The controlled epilepsy (CE) group (n = 20, 29.85%) included patients whose seizures were well controlled with ASMs and who were seizure-free for at least 3 months. The uncontrolled epilepsy (UCE) group (n = 47, 70.15%) included two subcategories of patients based on their response to ASMs: those with DRE (uncontrolled and drug-resistant) (n = 24, 35.82%) and those with non-drug-resistant epilepsy (NDRE) (uncontrolled but had not met the criteria for drug resistance) (n = 23, 34.33%) (Fig. 1). DRE was defined in the Introduction section. Those with NDRE included patients whose epilepsy remained uncontrolled after only one trial of an ASM or

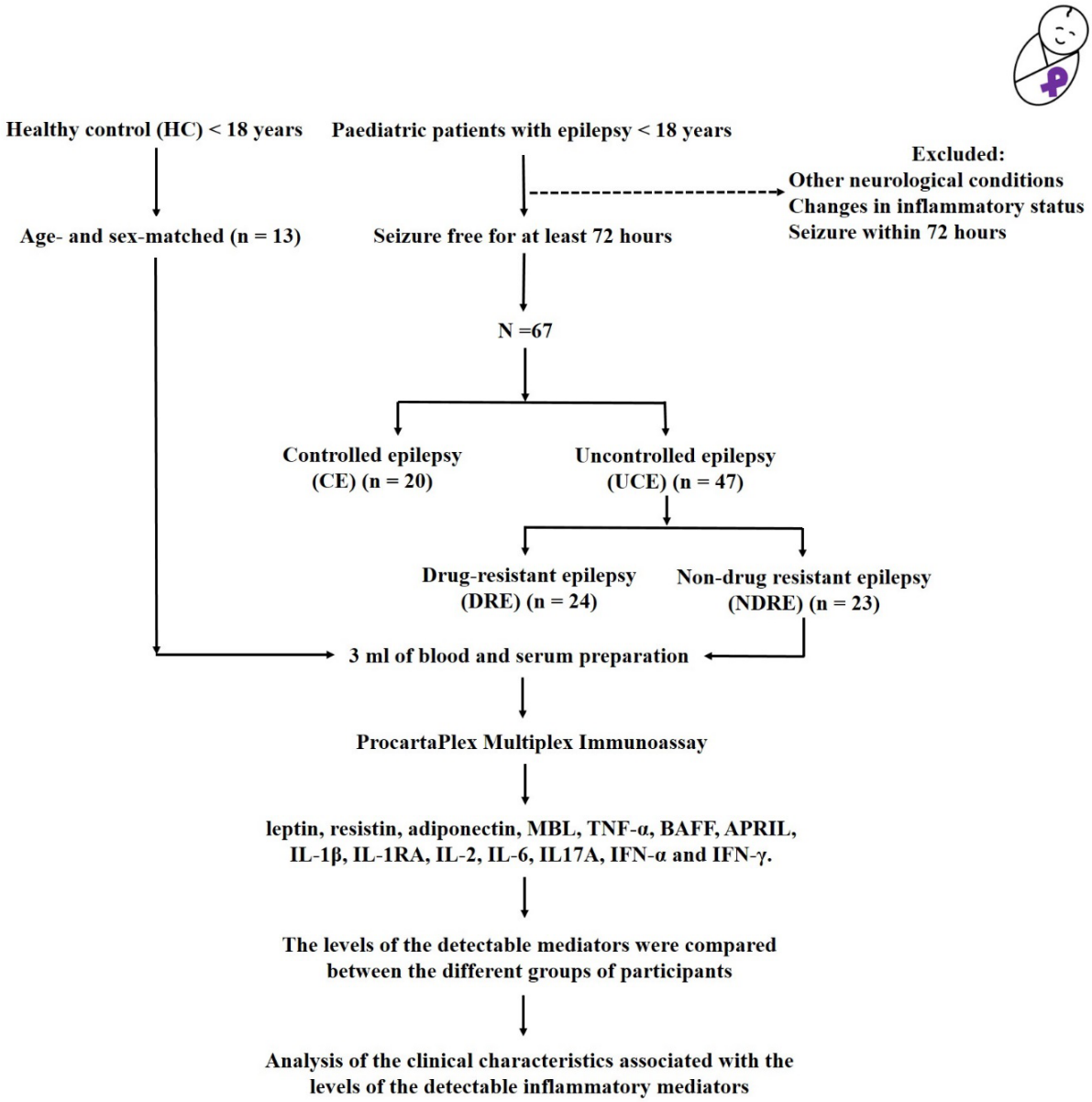

Figure 1. Flow chart of the study protocol.

two ASMs at doses below the maximum tolerated therapeutic doses and thus had not yet met the criteria for drug resistance (NDRE = UCE − DRE). In addition, a healthy control (HC) group of age- and sex-matched children was included in this study (n = 13).

Electronic medical records were used to collect patient demographics and medical history. These included age, sex, weight, height, age at onset and duration of epilepsy, time since the last seizure, type of epilepsy (focal or generalized), MRI findings (if available), number of ASMs used, and the presence or absence of developmental delay. Assessment of seizure severity was also conducted using the 7-item National Hospital Seizure Severity Scale (NHS3) (O'Donoghue et al. 1996), which was previously applied to pediatric patients with epilepsy (Gakharia et al. 2022). This scale was applied to children aged 6 years and older, as some items were not applicable to children younger than 6 years, such as the assessment of urinary incontinence during seizures. The score was assessed for all types of seizures experienced by each patient, and the worst score was selected for further analysis. Parents, medical records, and the pediatric neurologist were consulted during data collection. Ethical approval of the study protocol—including blood collection from children—was obtained from the research committee at the University of Jordan Hospital (IRB no. 328/2019). Informed consent was obtained from all parents/caregivers. This study was conducted in accordance with the Declaration of Helsinki and applicable national regulations.

Blood samples (3 mL) were collected from the children during routine laboratory testing after obtaining written consent from their parents/caregivers. The blood was used for serum preparation and then for immunoassays. A qualified nurse performed blood collection.

Serum preparation

A volume of 3 mL of blood was collected from each patient into a silica-gel serum separator tube. Blood samples were left at room temperature for 30 min to clot, followed by centrifugation at 3000 rpm for 10 min at 4 °C. Serum samples were aliquoted and frozen at −80 °C immediately after collection.

Multiplex immunoassay

The inflammatory mediators investigated in this study were leptin, resistin, adiponectin, MBL, TNF-α, BAFF, APRIL, IL-1β, IL-1RA, IL-2, IL-6, IL-17A, IFN-α, and IFN-γ. The serum levels of these mediators were evaluated using the human ProcartaPlex Multiplex Immunoassay (Invitrogen, Thermo Fisher Scientific, Austria) according to the manufacturer's protocol. A volume of 25 µL of undiluted serum was used for all assays, except for the MBL and adiponectin assays, for which a dilution factor of 1:500 was used. Samples were analyzed using the Bio-Plex 200 System (Bio-Rad, USA). Data were analyzed using Bio-Plex Manager v. 6.2.0.175 software (Bio-Rad, USA).

Statistical analysis

Statistical analysis was carried out using SPSS software v. 27.0.1 (SPSS Inc., Chicago, IL, USA). Graphical presentations were prepared using Prism v. 9 software (GraphPad Software, Inc., California, USA). Categorical variables were presented as percentages with frequencies, whereas continuous variables were presented as means ± standard deviation (SD). Continuous variables were tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Pearson's chi-square or Spearman's correlation tests were conducted to determine associations between categorical or continuous variables, respectively. The Mann–Whitney *U* test or Kruskal–Wallis tests were employed to determine between-group differences. A *p*-value of <0.05 was regarded as statistically significant. Multiple binary logistic regression analysis was performed to identify inflammatory mediators predictive of DRE in children with epilepsy. The covariates that were identified through bivariate analyses as being significantly associated with the outcome measure of DRE were entered into this model. In this analysis, patients without DRE (including those with CE and those with uncontrolled NDRE) were coded as 0, while those with DRE were coded as 1. In addition, stepwise multiple linear regression analysis was employed to identify predictors of the outcome measure of higher cytokine levels. The factors that were found to be significantly associated with each cytokine level through bivariate analyses were entered into the regression analysis.

Results

Demographics and general characteristics of the study population

The eligible pediatric patients with epilepsy included in the study had an average age of 9.02 years (0.1–17 years) and a BMI of 20.24 kg/m^2 (Table 1). No significant differences were found between the patients and the healthy controls in terms of age, weight, height, BMI, and sex.

Comparative analysis of the levels of adipokines in healthy children, children with epilepsy, and the different groups of epilepsy patients

Serum levels of leptin, adiponectin, and resistin were significantly altered in patients with epilepsy compared with the HC group (p = 0.022, 0.045, and 0.009, respectively) (Fig. 2a, d, g). Leptin and adiponectin levels were significantly higher in patients with epilepsy compared with their levels in the HC group, while resistin levels were significantly lower in patients with epilepsy compared with the HC group.

Between-group comparisons showed that leptin levels did not differ significantly between DRE and NDRE (Fig. 2b) or between CE and UCE (Fig. 2c). However, comparisons of the patient groups with the HC group showed that leptin levels were significantly higher only in the DRE group compared with the HC group (p = 0.031) (Fig. 2b). Regarding adiponectin, its level in the UCE group was significantly higher than that in the CE group (p = 0.008) (Fig. 2f). More specifically, within the UCE group, the DRE group—but not the NDRE group—showed a significantly higher level of adiponectin compared with the CE group (p = 0.018) or the HC group (p = 0.022) (Fig. 2e). Resistin levels were significantly higher in the

Table 1. General characteristics of the study population.

Parameter (mean ± SD)	Healthy control (n = 13)	Epilepsy patients (n = 67)	P-value*
Age (year) [a]	8.00 ± 3.34	9.02 ± 4.83	0.364
Weight (kg) [a]	30.45 ± 15.45	36.94 ± 21.42	0.348
Height (cm) [a]	126.92 ± 20.66	126.17 ± 32.27	0.756
BMI (kg/m2) [a]	18.19 ± 5.33	20.24 ± 5.80	0.292
Gender [b]			
Male n (%)	6 (46.2)	39 (58.8)	0.423
Female n (%)	7 (53.8)	28 (41.8)	

SD: standard deviation; a Mann–Whitney U test; b Pearson chi-square test; *Significant at P < 0.05.

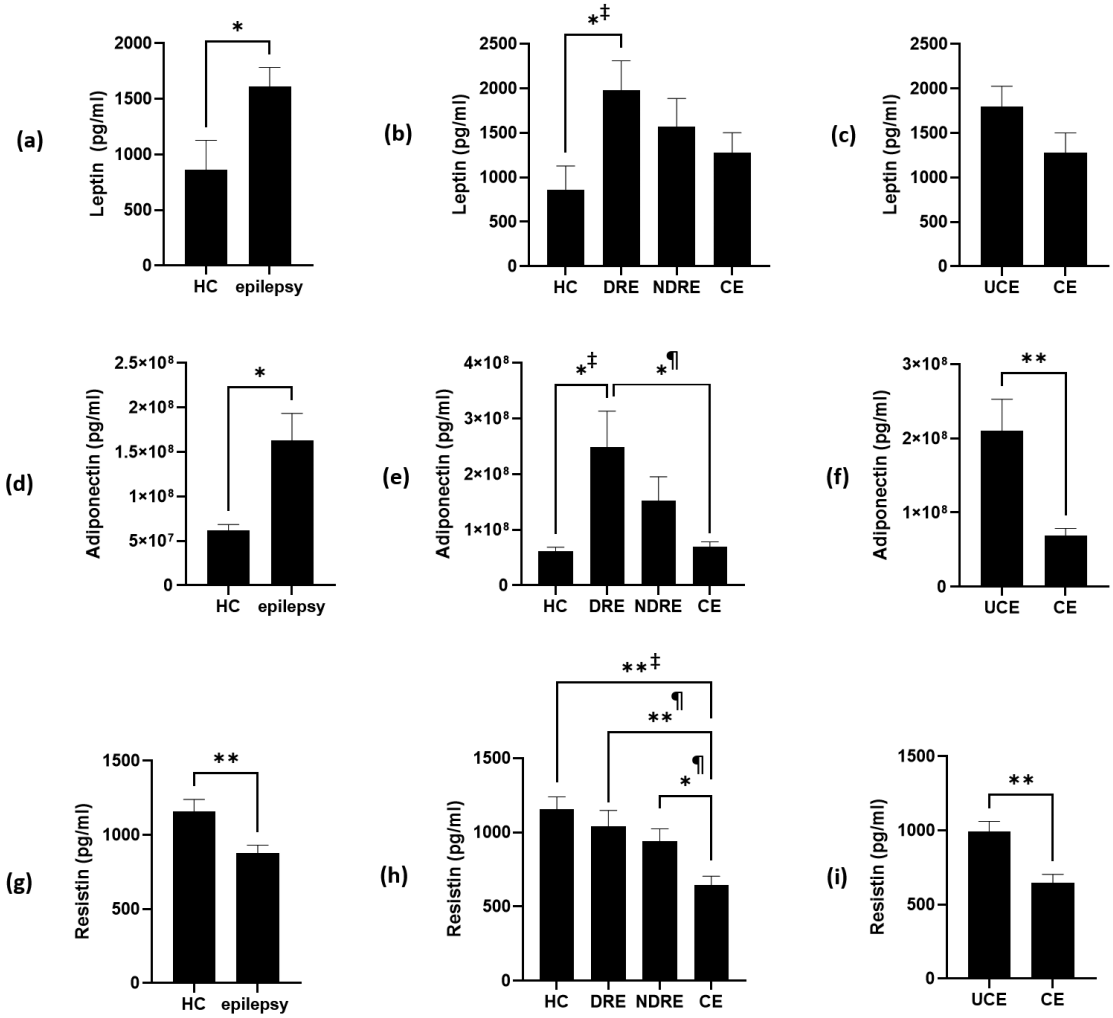

Figure 2. Serum levels of adipokines in healthy controls, patients with epilepsy, and the different groups of epilepsy patients. **a–c.** Leptin levels; **d–f.** Adiponectin levels; **g–i.** Resistin levels. CE: controlled epilepsy; DRE: drug-resistant epilepsy; HC: healthy control; NDRE: non-drug-resistant uncontrolled epilepsy. Multiplex ELISA immunoassays were conducted (data represent mean ± SEM; at least 13 samples were used for each group; Mann–Whitney *U* or Kruskal–Wallis tests; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). ‡ Compared with the HC group; ❡ as per between-group comparison.

UCE group compared with the CE group ($p = 0.002$) (Fig. 2i), with both NDRE ($p = 0.037$) and, to a greater extent, DRE ($p = 0.009$) within the UCE group demonstrating significantly higher levels of resistin compared with the CE group (Fig. 2h). In addition, resistin levels were lowest in the CE group among the different patient groups and were significantly lower than those in the HC group ($p = 0.001$) (Fig. 2h).

Comparative analysis of the levels of TNF-α, MBL, and other inflammatory mediators in healthy children, children with epilepsy, and the different groups of epilepsy patients

The serum levels of TNF-α and MBL did not differ significantly between patients with epilepsy and the HC group (Fig. 3a, d) or between the different patient groups (Fig. 3b, c, e, f), with the exception of TNF-α levels, which were significantly higher in the DRE group compared with the NDRE ($p = 0.040$) or CE ($p = 0.046$) groups.

The serum levels of the other cytokines investigated, including BAFF, APRIL, IL-1β, IL-1RA, IL-2, IL-6, IL-17A, IFN-α, and IFN-γ, were all undetectable.

Inflammatory mediators predictive of DRE among children with epilepsy

As presented in Table 2, DRE was associated with significantly higher levels of resistin, adiponectin, and TNF-α compared with other patients with epilepsy (Table 2a). These potential predictors were entered into a multiple binary logistic regression analysis, which showed that only resistin and TNF-α had significant predictive value for DRE. Patients with higher levels of resistin or TNF-α were one time or approximately eight times more likely to have DRE, respectively, compared with other patients with epilepsy (Table 2b).

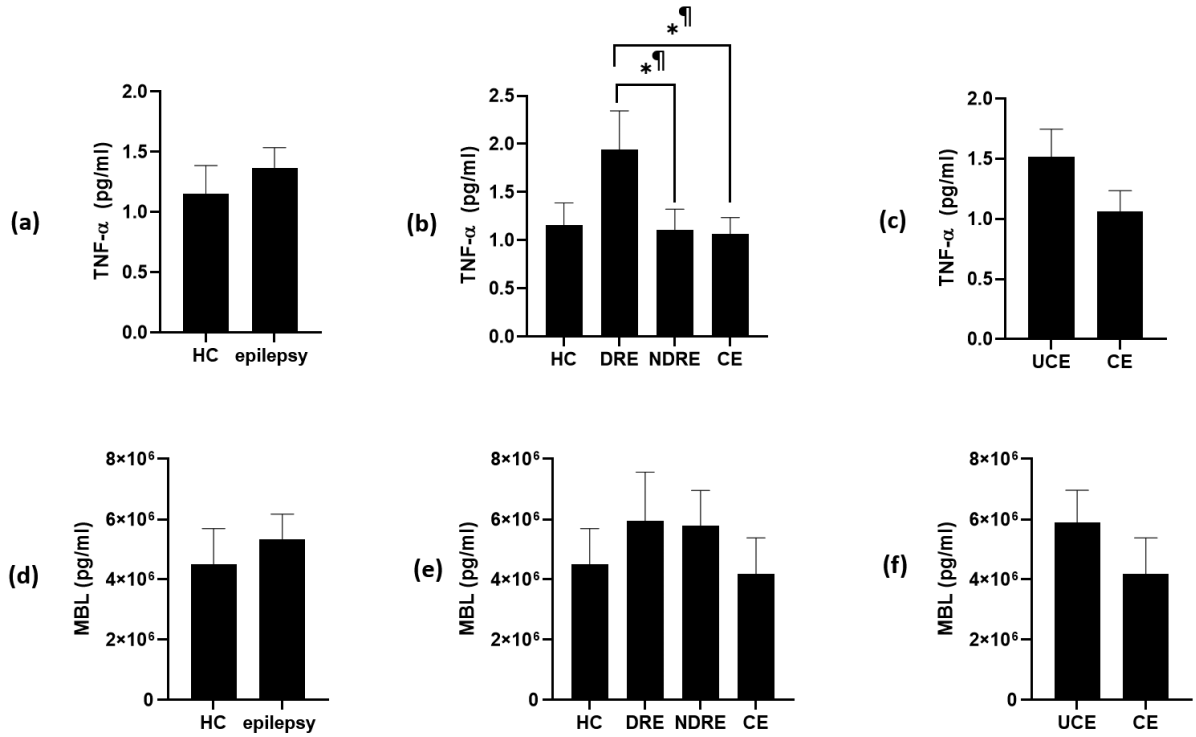

Figure 3. Serum levels of TNF-α and MBL in healthy controls, patients with epilepsy, and the different groups of epilepsy patients. **a–c.** TNF-α levels; **d–f.** MBL levels. CE: controlled epilepsy; DRE: drug-resistant epilepsy; HC: healthy control; NDRE: non-drug-resistant uncontrolled epilepsy. Multiplex ELISA immunoassays were conducted (data represent mean ± SEM; at least 13 samples were used for each group; Mann–Whitney *U* or Kruskal–Wallis tests; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). ¶ as per between-group comparison.

Table 2. Adipokines, TNF-α, and MBL levels in patients with DRE compared with other patients with epilepsy and inflammatory mediators predictive of DRE.

a. Adipokines, TNF-α, and MBL levels.					
	DRE[a]	**Other epilepsy patients**		***p*-value**	
Leptin	1976.85 ± 1556.93	1412.09 ± 1169.15		0.08	
Resistin	1041.97 ± 499.07	790.06 ± 350.73		**0.048***	
Adiponectin	$2.5 \times 10^8 \pm 2.76 \times 10^8$	$1.06 \times 10^8 \pm 1.10 \times 10^8$		**0.022***	
TNF-α	1.94 ± 1.75	1.09 ± 0.85		**0.005****	
MBL	$5.94 \times 10^6 \pm 7.56 \times 10^6$	$4.92 \times 10^6 \pm 4.66 \times 10^6$		0.814	
b. A multiple binary logistic regression results to identify the predictor inflammatory mediators of DRE in children with epilepsy.					
	B	**SE**	***p*-value**	**OR**	**95% C.I.**
Resistin	0.003	0.001	**0.044***	1.003	1.000–1.005
Adiponectin	0.000	0.000	0.079	1.000	1.000–1.000
TNF-α	2.070	0.823	**0.012***	7.924	1.578–39.800
Constant	-6.472	2.186	0.003	0.002	

B: unstandardized regression coefficient; CI: confidence interval; DRE: drug-resistant epilepsy; OR: odds ratio; SD: standard deviation; SE: standard error.
[a]Data represent mean ± SD; at least 18 samples were used for each group; Mann–Whitney *U* test; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

Clinical characteristics of epilepsy patients and their associations with the levels of inflammatory mediators

Clinical characteristics of the patients and the mean levels of inflammatory mediators are summarized in Table 3. On average, epilepsy was diagnosed at an age of 4.78 years and had a duration of 3.96 years, with an average time since the last seizure of 206 days (~7 months). Almost two-thirds of the patients had generalized epilepsy, had abnormal MRI findings, and did not show developmental delay, while one-third had focal epilepsy, had normal MRI findings, and showed developmental delay. Almost equal proportions of the patients received ASM monotherapy or combination therapy.

Regarding the factors associated with the levels of inflammatory mediators, leptin and resistin levels were positively correlated with patients' age, weight, and height. Leptin levels were also positively correlated with patients' BMI. Ad-

Table 3. Clinical parameters of patients with epilepsy and their association with inflammatory mediator levels (n = 67).

Clinical characteristic		Leptin 1612.49 ± 1335.16 pg/ml[a] (p-value)[f]	Resistin 878.02 ± 422.35 pg/ml[a] (p-value)[f]	Adiponectin 1.63 × 10^8 ± 2.04 × 10^8 pg/ml[a] (p-value)[f]	TNF-α 1.37 ± 1.27 pg/ml[a] (p-value)[f]	MBL 5.34 × 10^6 ± 6.00 × 10^6 pg/ml[a] (p-value)[f]
Age (years)[a, b]	9.02 ± 4.83	**0.003 (0.366)****	**0.006 (0.340)****	**0.047 (-0.289)***	0.173 (-0.181)	0.579 (-0.078)
Weight (kg)[a, b]	36.94 ± 21.42	**0.001 (0.421)****	**0.002 (0.391)****	**<0.001(-0.500)*****	0.367 (-0.121)	0.295 (-0.147)
Height (m)[a, b]	126.17 ± 32.27	**0.000 (0.442)*****	**0.009 (0.326)****	**0.002 (-0.457)****	0.311 (-0.135)	0.572 (-0.080)
BMI (kg/m2)[a, b]	20.24 ± 5.80	**< 0.001(0.440)*****	0.141 (0.191)	**0.003 (-0.448)****	0.567 (-0.078)	0.767 (0.043)
Epilepsy early age (years)[a, b]	4.78 ± 4.57	**0.049 (0.251)***	**0.029 (0.275)***	0.061 (-0.282)	0.331 (-0.130)	0.785 (-0.038)
Duration of epilepsy[a, b]	3.96 ± 3.75	0.287 (0.137)	0.497 (0.087)	0.689 (-0.061)	0.95 (0.008)	0.827 (0.031)
Duration of time since last seizure (days)[a, b]	206.11 ± 431.51	0.176 (-0.176)	**0.016(-0.305)***	**0.004 (-0.422)****	0.652 (-0.061)	0.178 (-0.190)
Seizure severity (NHS3 score)[b, c]	9.50 ± 4.85	0.245 (0.175)	0.855 (0.028)	0.104 (0.293)	0.271 (-0.176)	0.374 (0.146)
Epilepsy type [d]						
Focal, n (%)	28 (41.8)	0.797	0.18	0.375	0.377	0.183
Generalized, n (%)	39 (58.2%)					
MRI [d, e]						
Normal, n (%)	20 (35.71)	1	0.617	0.612	0.701	0.106
Abnormal, n (%)	36 (64.29)					
ASM [d]						
Monotherapy, n (%)	32 (47.8)	0.125	0.417	0.073	**0.003****	0.950
Combination therapy, n (%)	35 (52.2)					
Having Developmental delay [d]						
Yes, n (%)	27 (40.3)	0.977	0.653	**0.009****	0.507	0.590
No, n (%)	40 (59.7)					

ASM: antiseizure medications; BMI: body mass index; NHS3: National Hospital Seizure Severity Scale; SD: standard deviation.
[a]Data are presented as mean ± SD, [b]Spearman correlation,[c]NHS3 score of the worst seizure for those at the age of 6 years and older
[d]Mann–Whitney U test, [e]Valid percent. [f]P-value is presented with Spearman's correlation coefficient, *P value < 0.05, **P value < 0.01, ***P value < 0.001

iponectin levels, however, were negatively correlated with patients' age, weight, height, and BMI. Regarding epilepsy features, leptin and resistin levels—but not adiponectin levels—were positively correlated with age at epilepsy onset. Adiponectin and resistin levels were negatively correlated with the time since the last seizure (indicating better epilepsy control). This is consistent with the results regarding the levels of these adipokines in the CE group, as shown in Fig. 2f and Fig. 2i, respectively, where their levels were lower in the CE group compared with the UCE group. Of the three adipokines, only adiponectin levels were significantly correlated with developmental delay status. A mean level of $1.00 \times 10^8 \pm 0.93 \times 10^8$ pg/mL was observed in those without developmental delay, while a mean level of $2.4 \times 10^8 \pm 2.71 \times 10^8$ pg/mL was observed in those with developmental delay.

The levels of TNF-α and MBL were not correlated with any of the patients' characteristics, with the exception of the use of combination therapy, which was significantly correlated with TNF-α levels, with a mean level of 1.71 ± 1.48 pg/mL in the combination therapy group compared with 0.99 ± 0.87 pg/mL in the monotherapy group.

Regarding correlations among the levels of different mediators, only leptin levels were positively correlated with resistin levels (p = 0.02, correlation coefficient = 0.3) and MBL levels (p = 0.039, correlation coefficient = 0.295).

Predictors of the levels of leptin, resistin, and adiponectin in children with epilepsy

Factors that were associated with cytokine levels, as indicated in the section "Clinical characteristics of epilepsy patients and their associations with the levels of inflammatory mediators," were entered into stepwise multiple linear regression analysis to identify the factors most likely to predict the levels of the corresponding adipokines in pediatric patients with epilepsy. The results of regression analysis for leptin (R^2 = 0.337, p = 0.043), resistin (R^2 = 0.262, p = 0.044), and adiponectin (R^2 = 0.359, p = 0.022) are presented in Table 4. BMI, MBL levels, and resistin levels had the strongest positive associations with leptin levels among all the factors analyzed. Regarding resistin, patient age and leptin levels were positively associated with resistin levels, while a negative correlation was observed with the time since the last seizure. Regarding adiponectin, the presence of developmental delay was the only factor positively associated with adiponectin levels, while weight was the only factor negatively associated with adiponectin levels. Of note, height was excluded from the models for all three adipokines because of multicollinearity with age.

Table 4. Multiple linear regression models for predictors of leptin, resistin, and adiponectin levels in children with epilepsy.

	Predictor	SE	B	t	*P*-value
Leptin	BMI	29.709	0.325	2.549	**0.015**
	MBL level	0.000	0.333	2.645	**0.011**
	Resistin level	0.398	0.266	2.091	**0.043**
Resistin	Age (years)	10.936	0.327	2.671	**0.010**
	Duration of time since last seizure	0.109	−0.280	−2.380	**0.021**
	Leptin level	0.037	0.249	2.060	**0.044**
Adiponectin	Weight (Kg)	1169520.260	−0.472	−3.682	**0.001**
	Having developmental delay	53416272.111	0.305	2.379	**0.022**

B: unstandardized regression coefficient; SE: standard error; *t*: *t*-test statistic.

Discussion

Neuroinflammation involving alterations in the levels of several proinflammatory cytokines and adipokines has been suggested to be involved in the pathogenesis of epilepsy. Inconsistent findings have been reported regarding the types and levels of these inflammatory mediators and adipokines in epilepsy, including DRE (Palmio et al. 2016; Ethemoglu et al. 2018; Shan et al. 2023; Zawadzka et al. 2025). Therefore, this report presents a comprehensive comparison of the levels of leptin, adiponectin, resistin, and several inflammatory mediators in pediatric patients with epilepsy in relation to the control status and drug resistance status of the patients and in comparison with healthy controls. In addition, the inflammatory mediators associated with a higher risk of DRE and the factors associated with the levels of the different mediators were identified.

Leptin, adiponectin, and resistin have innate and adaptive immunomodulatory effects in addition to their neuroprotective effects (Tilg and Moschen 2006; Shan et al. 2023). Leptin, in particular, also has proconvulsant activity (Tilg and Moschen 2006; Shan et al. 2023). Considering all pediatric patients with epilepsy in this study, who were seizure-free for at least 72 h, leptin and adiponectin levels were significantly higher than those in the HC group, while resistin levels were significantly lower. Similar findings from previous reports support these results; however, these studies were carried out in adult populations or in patients with different epilepsy statuses (i.e., TLE, newly diagnosed epilepsy, within 24 h of a tonic-clonic seizure, or febrile seizures) (Palmio et al. 2016; Toscano et al. 2019; Parveen et al. 2024). For instance, consistent with the present results, a previous report in a population of adults with TLE showed higher levels of leptin and lower levels of resistin, whereas, in contrast to the present results, it showed decreased levels of adiponectin compared with the controls (Toscano et al. 2019). Similar to the present results, elevated serum levels of leptin were also demonstrated in newly diagnosed, untreated adolescents and adults with epilepsy compared with healthy controls (Parveen et al. 2024). Regarding adiponectin, similar to the present results, elevated levels of adiponectin were observed in adult populations during the acute seizure phase (within 24 h) following a tonic-clonic seizure (Palmio et al. 2016) or in children with febrile seizures (Chen et al. 2020). Notably, studies that specifically addressed adipokine levels in pediatric epilepsy focused on the impact of treatment with a specific ASM or a ketogenic diet on the levels of these adipokines, and thus it was difficult to directly compare the findings of the present study with those of previous studies (Sidhu et al. 2017; Nisha et al. 2018; Chyra et al. 2021). In conclusion, the present study, in contrast to the aforementioned studies, specifically focused on adipokine levels in the pediatric population outside the acute seizure phase, regardless of the specific treatment administered.

In this study, a gradual increase in the levels of the three adipokines was observed with the loss of epilepsy control and with drug resistance. Considering the DRE group, the serum levels of leptin, adiponectin, and resistin were higher than those in the uncontrolled NDRE and CE groups. However, significant differences compared with CE were observed only for adiponectin and resistin, but not leptin. Previous studies that investigated the levels of adipokines in DRE mainly focused on the impact of a specific treatment strategy, i.e., the ketogenic diet, on adipokine levels in DRE or were conducted in adult populations (Ethemoglu et al. 2018; Chyra et al. 2021, 2022). However, the present study provides, for the first time, a broader understanding of adipokine levels in DRE in the pediatric population, regardless of the impact of any particular treatment approach. For instance, in children with DRE, similar to the present findings, adiponectin and resistin levels were significantly higher, while leptin levels, in contrast to the present results, were lower in patients treated with a ketogenic diet compared with those treated with valproic acid or healthy controls (Chyra et al. 2021, 2022). In adult populations, in contrast to the present results, adiponectin levels were significantly reduced compared with those in patients with controlled epilepsy or healthy controls (Ethemoglu et al. 2018). The differences between the present results and those reported in the literature could be explained by the different settings employed in the various studies, including age groups and antiseizure treatments used. In this report, when comparing the CE and UCE groups (DRE and

NDRE), the levels of the three adipokines were reduced in patients with controlled epilepsy compared with those with UCE, although the reduction in leptin levels was not statistically significant. The present results in this regard were similar to those of a previous report in which adiponectin levels, but not leptin levels, were significantly reduced in patients with epilepsy following treatment with valproic acid for 1 year compared with baseline (Sidhu et al. 2017). The reduced levels of adipokines in the CE group could be explained by the therapeutic effects of ASMs, which reduced the levels of adipokines and inflammatory cytokines in patients with drug-responsive epilepsy, resulting in improved epilepsy control (Abu-Rish et al. 2017, 2018, 2020; Sidhu et al. 2017).

In drug-resistant epilepsy, neuroinflammation involving innate and adaptive immune mechanisms has been documented (Shi et al. 2025). Regarding inflammatory cytokines, the present findings demonstrated a significant association between TNF-α levels and DRE. TNF-α levels were significantly higher in the DRE group compared with the uncontrolled NDRE or CE group. The present study also showed, for the first time, that TNF-α levels were significantly correlated with the use of combination therapy (Table 3), with all patients with DRE in this study receiving combination therapy. Similarly, elevated levels of TNF-α were previously shown in adults with TLE and DRE (Sokolova et al. 2022) and in children with DRE (Kamaşak et al. 2020). However, other reports, despite showing elevated serum levels of TNF-α compared with healthy controls, did not specify whether the patients had DRE or whether the levels were correlated with the number of ASMs used (Choi et al. 2020) or were conducted in children with controlled epilepsy rather than DRE (Elhady et al. 2022). Moreover, another report in adults demonstrated no significant differences in the serum levels of TNF-α (in addition to IL-1β and IL-6) in patients with TLE compared with healthy controls, and there were no significant differences between DRE and NDRE in the levels of these cytokines (Milano et al. 2024). Therefore, considering the aforementioned variable findings in the literature, the present results demonstrated significantly elevated TNF-α levels in DRE, which were also correlated with the use of combination therapy. Regarding the other cytokines investigated in this study, undetectable levels of IL-1β, IL-1RA, IL-2, IL-6, IL-17A, IFN-α, and IFN-γ were demonstrated in the serum of pediatric patients with epilepsy. However, previous reports in adults and children demonstrated elevated or reduced levels, or no changes in the levels, of several of these cytokines in epilepsy under different settings (Choi et al. 2020; Kamaşak et al. 2020; Toledo et al. 2021; Elhady et al. 2022; Sokolova et al. 2022; Diler Durgut et al. 2025). Regarding MBL, evidence implicating the complement system in the pathogenesis of epilepsy in adults was previously provided (Kopczynska et al. 2018). In addition, high MBL levels were associated with an increased frequency of seizures in patients with systemic lupus erythematosus (Cieslinski et al. 2018).In this study, MBL levels were tested in patients with epilepsy for the first time; however, the levels did not differ significantly between patients with epilepsy and the HC group or among the different groups of patients with epilepsy. Concerning the role of the BAFF–APRIL system in the pathogenesis of epilepsy, the results of a previous report showed that in patients with intractable TLE, BAFF and BAFFR expression levels were markedly upregulated, suggesting a role in the regulation of epilepsy pathogenesis (Ma et al. 2017). Therefore, in the present study, to identify any possible role of this system in the pathogenesis of pediatric epilepsy, the serum levels of BAFF and APRIL proteins were investigated; however, both were found to be undetectable.

As mentioned above, in the DRE group, the levels of leptin, adiponectin, resistin, and TNF-α were higher than those in the uncontrolled NDRE or CE groups. However, comparison of the DRE group with all other patients with epilepsy in this study (uncontrolled NDRE and CE) demonstrated significantly higher levels of resistin, adiponectin, and TNF-α, but the increase in leptin levels was not statistically significant. Multiple binary logistic regression analysis showed that only resistin and TNF-α had significant predictive value for DRE compared with other patients with epilepsy.

Regarding the correlations between cytokine levels and the clinical parameters of the patients, the present study demonstrated that leptin and resistin levels showed significant positive correlations with patients' age, weight, and height, while adiponectin levels showed significant negative correlations with the aforementioned clinical parameters. This could be explained by the fact that these adipokines regulate glucose metabolism and body weight (Tilg and Moschen 2006). The present results are consistent with a previous report that demonstrated a significant positive correlation of leptin levels with the weight and height of pediatric patients with epilepsy (Chyra et al. 2021) and that changes in leptin levels were positively correlated with changes in weight and body fat in patients with epilepsy after treatment with a classical ketogenic diet (De Amicis et al. 2019). A positive correlation of resistin levels and a negative correlation of adiponectin levels—although statistically insignificant—were previously demonstrated with the age, weight, and height of children with epilepsy (Chyra et al. 2021, 2022). Notably, leptin levels in this study were positively correlated with resistin levels, which could be explained by the crosstalk between these two adipokines in weight control. Adiponectin and resistin levels were found, for the first time, to be negatively correlated with the time since the last seizure; this indicates that their levels are lower in patients with a lower seizure frequency and better epilepsy control. This further confirms the lower levels of these adipokines in the CE group and their higher levels in the DRE group demonstrated in this study. The present study also showed, for the first time, that adiponectin levels were significantly higher in children with developmental delay. A previous report demonstrated that higher adiponectin levels predicted cognitive decline, although this was in patients with beta-amyloid pathology (Kim et al. 2022). Importantly, the

results of multiple linear regression analysis of the predictors of adipokine levels in children with epilepsy showed that MBL levels, resistin levels, and BMI were the strongest predictors of leptin levels. Regarding resistin, leptin levels, a shorter time since the last seizure, and age were the strongest predictors of higher resistin levels. Concerning adiponectin, the presence of developmental delay and lower patient weight predicted higher adiponectin levels.

Conclusion

This report presents findings regarding the role of leptin, resistin, adiponectin, and TNF-α as markers for distinguishing pediatric patients with different levels of epilepsy control and drug resistance status. In particular, resistin and TNF-α had significant predictive value for DRE. The main predictors of leptin levels were MBL levels, resistin levels, and BMI, while age, leptin levels, and a shorter time since the last seizure were the strongest predictors of higher resistin levels. The presence of developmental delay and lower patient weight predicted higher adiponectin levels. These findings provide new insights into understanding the pathogenesis of epilepsy and the development of new ASMs. However, the results should be generalized with caution because of the small sample size and the fact that the study was conducted at only one center.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

Ethical approval of the study protocol—including blood collection from children—was obtained from the research committee at the University of Jordan Hospital (IRB no. 328/2019). Informed consent was obtained from all parents/caregivers. This study was conducted in accordance with the Declaration of Helsinki and relevant national guidelines and regulations.

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: the University of Jordan hospital

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
No AI tools were used in the preparation of this manuscript.

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Author contributions

Study conception and design: E.Y.A. Data acquisition: E.Y.A., R.A., and A.M. Data analysis and interpretation: E.Y.A., A.M., R.A., Y.B., K.T., and Y.S.M. Writing of the manuscript: E.Y.A. Critical revision of the manuscript: E.Y.A., A.M., R.A., Y.B., K.T., and Y.S.M. All authors approved the submitted manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.