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Prostaglandin E2 as neuroinflammatory target in childhood resistant epilepsies.

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Abstract

Aim: Childhood epilepsies are a diverse group of neurological disorders with a multifaceted clinical course caused by a range of aetiological factors. Despite new Anti Seizure Drugs (ASDs), drug resistance remains a significant hurdle in treatment. Growing evidence links epilepsy to inflammatory processes, especially in drug-resistant cases. A number of neuroinflammatory pathways involving cytokines have been identified in the pathogenesis of drug resistant epilepsy, including the axis of Cox2–PGE2-Prostaglandin E2 receptor 1 that has been shown to affect blood-brain barrier function, and drug pharmacokinetics through upregulation of multidrug effluxers. We measured the plasma PGE2 levels aiming to determine PGE2 importance in epilepsy-associated inflammation and antiepileptic drug (AED) response for the patients with different types of epilepsy .

Methods: a prospective review of clinical and paraclinical data of study group (Group 1), including patients with epilepsy who had ongoing long term follow-up in two subgroups: Group 1A-Patients diagnosed with epilepsy -seizure-free on AED therapy, Group 1B- patients with refractory epilepsy and healthy control group (Group2). Serum samples tested for PGE2 levels(interquartile ranges/pg/ml) by the enzyme-linked immunosorbent assay (ELISA).

Results: Measured serum PGE2 the median interquartile ranges (IQR) were higher and in broader ranges for epilepsy patients all together 512 pg/ml (324.5-970.0)compared to healthy controls 406 pg/ml (278.7-541.4) , but not significantly different across the epilepsy study groups ($p>0.05$). Only Valproate responders showed reduced PGE2 mean IQR 490 pg/ml.

Conclusions: Our findings align with preclinical models, suggesting a potential target on molecular basis for overcoming drug resistance, which is a major challenge and key toward precision medicine in epilepsy management.

Keywords: Paediatric Epilepsy; Drug-resistant; Neuroinflammation

Introduction

Pediatric Epilepsy is a multifaceted neurological disorder with various etiology, which affects 0.6% of children between the ages of 0 and 17 years [1,2]. Antiepileptic drugs (AED) are the mainstay of treatment for childhood epilepsies, 90% cases of epilepsy in childhood is adhered to recommended AED treatment. With each subsequent unsuccessful AED regimen tries the likelihood of seizure freedom decreases significantly. Adequate seizure control is not achieved in 30% of patients, especially in epileptic encephalopathies which are considered drug-resistant [3]. The working hypothesis on drug resistance to be refined with time .Based on ILAE classification 2017 Drug-resistant or refractory seizures refer to "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" [4].

Despite many years of research, developing novel treatments and management strategies for drug resistance has been a longstanding goal ,cause modern AEDs could suppress seizures rather than modify the underlying disease and the mechanisms underlying drug resistance remain largely unknown. Thus, without exploring and rectifying the underlying neuropathological processes, epileptogenesis cannot be reversed.

Among other theories about current understanding of epileptogenesis, inflammation has been implicated in the pathogenesis of some types of epilepsy, including certain types of childhood epilepsies[5]. There is evidence of ongoing chronic neuroinflammation in epileptic areas, characterized by the activation of microglia, infiltration of immune cells, and increased production of pro-inflammatory mediators. Neuroinflammation can persist even after the initial trigger has resolved ,it can affect neuronal excitability, leads to blood-brain barrier (BBB) dysfunction,impacts on seizure threshold and,contributes to the development and progression of seizures [6]. According to the previous studies, cytokine accumulation and imbalances in epileptic tissue are markers of activated neuroinflammatory processes involving cerebral residents and recruited immune cells [7,8]. COX pathway metabolites such as prostaglandins, majorly PGE2, are known that could influence central neural inflammatory pathways and interfere mechanisms of epileptogenesis [9].

PGE2 may have indirect effects on seizure activity through its involvement in inflammation and neuronal excitability. As it known Cox-2 acts as rate-limiting enzyme for PGE2 production , due to influence of proinflammatory cytokines COX-2 expression is promptly induced in Blood-brain-barrier endothelium[10]. In several rodent models of drug-resistant epilepsy, blockade of the C0X2-PGE2 pathway, Prostaglandin E receptor 2 (EP2) receptor transitory inhibition reduced the degree of Blood-brain Barrier dysfunction, decreased cytokine production, reactive gliosis and seizure-promoted functional deficits thus appear having role in anti-inflammatory cascade and neuroprotection [11-14].

Amounting evidence also suggested that increased PGE2 biosynthesis following seizure may upregulate the multidrug efflux transporters, P-glycoproteins (P-gp), at hematoencephalic barrier[15]. This upregulation could contribute to an increased efflux of prescribed AEDs, potentially leading to reduced treatment efficacy. To treat epilepsy and to increase the effectiveness of AEDs, blocking this increase in PGE2 levels may be beneficial [16]. PGE2 biosynthesis could be affected by prescribed AEDs,

therefore Cyclooxygenase-2 and PGE2 receptor may proposed as target for new disease modifying treatments with goal to improve and restore seizure pharmacosensitivity and improve therapeutic outcomes [17,18].

However, the reported studies rely mostly on experimental evidence regarding immediate postictal changes in proinflammatory markers, but their role in the genesis of epilepsy and clinical phenotype or drug responsiveness is not clearly defined. AED resistance is very probably not caused by a single mechanism. Thus, exploring responsible biological pathway from bench to bedside is a major challenge towards precision medicine of epilepsy. In this case-control study we compared PGE2 levels (median, pg/ml) in sera of patients with different types of epilepsy. PGE2 profiles of patients on the basis of recieving drug and responsiveness were also analyzed, aiming to assess importance of epilepsy-associated inflammation and possible link with antiepileptic drug response ,which could be a new target biomarker in the future to develop therapies overcoming drug resistance.

Materials and methods

Participants were recruited from the Zhvania Academic Clinic of Pediatrics in Tbilisi, Georgia and grouped as follows: Group 1A consisted of seizure-free epilepsy patients on AED therapy for at least one year, Group 1B included subjects with drug-resistant epilepsies experiencing recurrent seizures despite treatment with two first-line AEDs and diagnosed with epileptic encephalopathies, and Group 2 comprised afebrile controls without neurological disorders, matched for age, gender, and ethnicity. Exclusion and inclusion criteria are detailed in Table 1.

The exclusion and inclusion criteria from study groups were as follows in Table 1.

Table 1: Study subject exclusion and inclusion criteria

Exclusion	Inclusion
acute somatic illnesses autoimmune diseases recent infections regular consumption of the COX-2-inhibiting drugs receiving nonsteroidal antiinflammatory drugs (NSAIDs) performing regular vigorous physical activity *	Age 0-16 Confirmed diagnosis of epilepsy

*defined by the Centers for Disease Control and Prevention [19].

Data Collection: Comprehensive systemic and neurological assessments, EEGs, and medical record reviews were conducted to gather demographic and clinical information, epilepsy subtype, disease duration, seizure types and outcomes, pre-existing investigations and treatment, including antiepileptic

medication usage and treatment response categorizations such as "Valproate responders" and "Valproate non-responders."

Blood Sample Collection: Venous blood samples were collected under sterile conditions, processed, and dispatched to the laboratory for further analysis, including systemic lab measurements and assessment of prescribed AED serum levels.

Cytokine Analysis: Prostaglandin E2 levels were measured using ELISA kits. Statistical analysis was performed using SPSS 21, with continuous variables presented as means ± SD for normal distribution and as median interquartile range (IQR) for nonparametric data. Data comparison utilized Kruskal–Wallis and Mann–Whitney U tests, and graphical representation was created using GraphPad Prism 8.

Ethical Considerations: The study adhered to the Declaration of Helsinki principles and was approved by the Tbilisi State Medical University research ethics committee (10.11.2019).

Results

Based on a retrospective review of clinical and paraclinical data patients with epilepsy who had ongoing long term follow-up and healthy control group , In total 56 patients aged 0–16 [20], were selected for study groups-: patients diagnosed with epilepsy -seizure-free on AED therapy N=20, refractory epilepsy patients N=20, and healthy controls N=16 .

Amongst 40 patients with epilepsy, mean follow-up duration 18.5(range 11- 24) months with 11 being refractory over mean of 5.6 (range 0.92-14)years [7 females; mean 8.3(range 4-11)years; 4 having at least seizure free periods [2 females; mean 10.5(range 7-14)years; mean time 12.2(range 8-120)months. Both pharmacosensitive and refractory groups did not differ on seizure semiology neither clinically, based on EEG or radiology. Refractory group had mean 15.7 ± 2.25 seizures . Pharmacosensitive group had a mean of 2.9± 0.59 seizures. Demographics and clinical characteristics of cohort is shortly outlined in Table 1.

Table 1: Demographics and clinical characteristics

	Group 1	Group 2A	Group 2B	VA responders	VA non-responders
N	16	20	20	11	14
Male/female ratio	8/8	12/8	9/11	7/4	9/5
Age (Mean + SD years)	9.2+4.0	8.5+4.6	9.2+4.2	7.1+3.2	6.2+4.2
Mean (IQR) follow-up duration (Months)	-	16.7 (2.5–22.3)	18.1 (3.2-20.5)	19.2 (8.2-24)	14.0 (7.0–17.0)

BMI (kg/m2), median (IQR)	22.0 (19.2–26.4)	20.9 (19.6–22.7)	20.5 (18.6–24.7)	20.3 (18.9–26.7)	19.2 (18.0–22.1)
Seizure type (N)					
Focal	-	4	2		–
Generalized	-	16	18	10	14
Epilepsy type (N)					
Idiopathic epilepsy		14	15	11	12
Symptomatic epilepsy		1	3	-	–
Drug dose [mg/day] Median (IQR)		-	145 (250–300)	250 (200–275)	300 (200–500)
Dosage [(mg/day)/kg]		22,2 (20.3–27.9)	29.9 (25–35,6)	33.1 (30–36,7)	33.8 (33.3–36.2)

N: number of samples; IQR: interquartile range; BMI: body mass index; VA: valproate.

Mean number of medications prior to becoming refractory was 3 (range 2-5). All the patients were treated by different AED were segregated on the basis of drug. Valproic acid was included in therapies of 14/20 resistant group and 11/20 patients of controlled epilepsy group. Overall, 53% (21/40) patients each from pharmacosensitive and refractory were on combination therapy of two AEDs. Our patients did not receive treatment involving a ketogenic diet or a vagus nerve stimulator.

Measured serum PGE2 the median interquartile ranges (IQR) were higher and in broader ranges for epilepsy patients all together 512 pg/ml (324.5-970.0)compared to healthy controls 406 pg/ml (278.7-541.4) , but not significantly different across the epilepsy study groups ($p>0.05$).

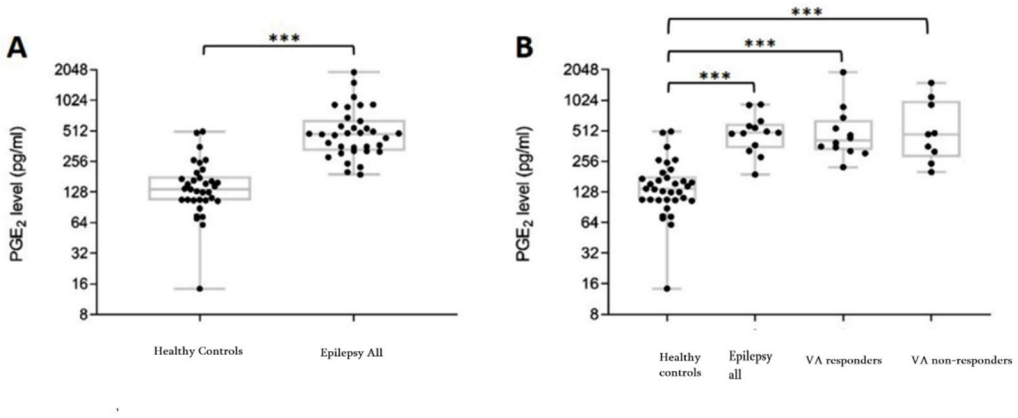

Figure 1. Comparison of plasma PGE2 levels A. "Healthy controls" vs all diagnosed with epilepsy; B. "Healthy controls" vs all diagnosed with epilepsy; and Valproate responsiveness subtypes – VA responders, VA non-responders.

Despite this valproate responders showed reduced PGE2 mean IQR 490 pg/ml in comparison to Valproate non-responders group. Corresponding data are given in Table 2.

Table 2: Plasma PGE2 levels in study groups:

Sample groups	IQR	Drug resistant	Pharmacosensitive	Healthy controls	VA responders	VA Non-responders
PGE2	Q1	324.2	388.0	278.0	240	256
	Q2	549.5	475.0	406.0	490	653
	Q3	970.0	595.0	541.0	820	970

IQR: interquartile range; VA: valproate.

Discussion

Recent studies by Vezzani et al. have shown an imbalance in cytokine levels in epileptic tissues, indicating a connection between epilepsy and inflammatory processes. This suggests that neuroinflammation may disrupt mechanisms of epileptogenesis by affecting seizure threshold and blood-brain barrier (BBB) function. [21]. Major inflammatory drivers in the brain include COX-2, IL-1β, TNF-α, TGF-β and CCL2 [22]. In epilepsy research, inflammation is often overlooked despite its potential significance. To address this gap, we investigated the role of interictal PGE2 levels in epilepsy-associated inflammation and drug response. Our study found varying PGE2 levels across different epilepsy groups, with refractory seizure patients showing higher levels compared to controlled seizure patients and healthy controls. Interestingly, Valproate responders exhibited lower PGE2 levels. These findings support the idea that PGE2 could be a promising target in overcoming drug resistance, aligning with preclinical models.

As it known, PGE2 is an essential pro-inflammatory mediator of Cyclooxygenase 2–Prostaglandin E2–Prostaglandin E2 Receptor 1 Axis, having role in neuroinflammation and Blood-Brain Barrier Dysfunction, which is could have been mechanisms involved in Drug Resistance [23].

Followed to seizures PGE2 release related effects has been discussed in many studies and the levels of PGE2 are known to elevate throughout the ongoing seizures and after[30]. A transitory blockade of the EP2 receptor in several rodent models resulted in a reduction in seizure-induced functional deficits and a decrease in cytokine production, gliosis, and BBB disruption, thereby exhibiting anti-inflammatory and neuroprotective effect [24].

While PGE2 is not typically associated with childhood epilepsies, it has been implicated in the pathophysiology of resistant seizures, particularly in cases of temporal lobe epilepsy (TLE),whereas Inflammatory processes have been identified as potential factors contributing to the development and maintenance of seizures [25] .Thus our results wide range of PGE2 levels in refractrory seizure group also could support idea of involvement these processes in mechanism of seizure refractoriness.

Although, PGE2 profiles of patients on the basis of recieving drug and responsiveness were analyzed, aiming to assess possible link with antiepileptic drug response. . In our study VA responders" had significantly lower PGE2.

Valproic acid (VPA)is primarily recognized as an antiepileptic and mood-stabilizing medication. While its primary mechanism of action is related to the modulation of neurotransmission, there is some evidence to suggest that valproate may have anti-inflammatory effects as well [26]. Valproate has been shown to reduce the activation of immune cells like microglia and astrocytes in the central nervous system , it decreases the production and release of certain pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [27]. These cytokines are key mediators of the inflammatory response, and their inhibition can help mitigate inflammation.

Valproic acid can modulate COX enzymes in the Arachidonic Acid Pathway. Valproate-responsive patients exhibit decreased COX-2 activity, leading to lower PGE2 levels. COX-2 is implicated in stimulating P-glycoprotein (P-gp), responsible for multidrug efflux. Studies have demonstrated that disruption of the BBB correlates with elevated COX-2 levels and PGE2 in epileptogenic areas, along with P-gp induction by brain vessels and astrocytes. In drug-resistant mesial TLE patients, a close association was found between COX-2 expression in neurons and glia, COX-1 expression in microglia, and P-gp and BCRP expression in small blood vessels. COX-2-induced upregulation of P-gp is mediated by NMDA receptors, Ca2+-dependent activation of phospholipase A2, arachidonic acid release, and COX-2-mediated production of PGE2 acting on the EP1 receptor [28].

Thus, AEDs can reduce COX-2 expression and may cause a suppression of P-gp overexpression, thereby facilitating the passage of drugs across the blood-brain barrier (BBB) and increasing the effectiveness of those drugs. In this manner Cyclooxygenase-2 and PGE2 receptors thereby holding promise in translational possibility with goal to improve and restore seizure pharmacosensitivity and better epilepsy management [29-31]. It may therefore be the reason why valproate responders exhibit lower levels of PGE2 in our study groups.

It's important to note that while there is limited clinical studies some research on the potential effects of valproic acid on cytokine levels, the precise mechanisms and clinical significance of these effects are not fully elucidated. The effects of valproic acid on PGE2 levels can vary among individuals [32]. Genetic factors, underlying medical conditions, and the specific dosage and duration of valproic acid treatment can all contribute to variability in its effects. More research is needed to understand the specific interactions in various contexts.Any potential interactions should be considered within the broader context of a patient's medical condition and treatment plan, based on their specific clinical response., the anti-inflammatory effects of valproate are not as well-established as its primary therapeutic actions, if confirmed through further research anti-inflammatory properties could be considered as secondary benefit in the management of epilepsy.

To the best of our knowledge, our study is the pilot report of the possible association between plasma PGE2 levels and epilepsy and drug response. The study presented certain limitations, including a small sample size and the assessment of cytokine levels at only a single time point during the interictal period. Treatment resistance is very probably not caused by a single mechanism .but our findings support the evidence that Inflammatory pathways could have impact on antiepileptic drug response. Limited clinical trial experience is supportive but not definitive for a role of the COX signaling cascade in epileptogenesis. Future work may emphasize on validating the findings in In the expanded and time-extended cohort of patients. Furthermore, molecular mechanisms underlying the role of COX-2 or PGE2 in AED efficacy needs to be explored as a new target system for pharmacological intervention to inhibit seizures by interfering with neuroinflammatory mechanisms involved in seizure genesis and recurrence . It is of paramount importance to gain a comprehensive understanding of the extended-term clinical trajectories and potential on molecular basis for overcoming drug resistance, ideally guided by biomarker of patient’s failure to seizure freedom ,which is a major challenge and key toward precision medicine in epilepsy management.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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აბსტრაქტი

ეპილეფსია ბავშვთა ასაკში წარმოადგენს ნევროლოგიურად ჰეტეროგენურ ჯგუფს, რომელსაც აქვს მულტიფაქტორული ეტიოლოგია და ხასიათდება სხვადასხვა კლინიკური მიმდინარეობით. ახალი გულყრის საწინააღმდეგო მედიკამენტების შექმნის მიუხედავად, მკურნალობის მნიშვნელოვან დაბრკოლებად წამლისადმი რეზისტენტობა რჩება. მზარდია მტკიცებულებები ეპილეფსიის ანთებით პროცესებთან კავშირის შესახებ, განსაკუთრებით წამლებისადმი რეზისტენტული ფორმების შემთხვევებში. რეზისტენტული ეპილეფსიის პათოგენეზში შესწავლილია ნეიროანთებითი გზები და ციტოკინების როლი, მათ შორის, ერთ-ერთი მნიშვნელოვანი რგოლია Cox2-PGE2-პროსტაგლანდინ E2 რეცეპტორ 1-ის ღერძი, რომელიც გავლენას ახდენს ჰემატოენცეფალური ბარიერის ფუნქციონირებაზე და ასევე უშუალოდ წამლის ფარმაკოკინეტიკაზე , პლაზმურ მემბრანიდან მედიკამენტების გამომფრქვევზე ზემოქმედების რეგულაციის გზით . კვლევის ფარგლებში, სისხლის შრატში განისაზღვრა PGE2 დონეები სხვადასხვა ტიპის ეპილეფსიის მქონე პაციენტებისთვის, რათა შეფასებულიყო PGE2 მნიშვნელობა ეპილეფსიასთან ასოცირებულ ანთებასა და ანტიეპილეფსიური წამლით მკურნალობის ეფექტურობაში .

მეთოდები: კლინიკური და პარაკლინიკური მონაცემების პერსპექტული ანალიზი, საკვლევი ჯგუფი 1 A-პაციენტები ეპილეფსიის დიაგნოზით - რომლებიც იტარებდნენ ანტიეპილეფსიურ მკურნალობას, მიმდინარე გულყრების გარეშე, ჯგუფი 1B- პაციენტები წამალ-რეზისტენტული ეპილეფსიით, ინტერიქტულ პერიოდში; საკონტროლო ჯგუფი 2 - ჯანმრთელ ბავშვები. შრატში PGE2 რაოდენობივი დონის (კვარტლთაშორისი დიაპაზონი/პგ/მლ) განსაზღვრა ფერმენტთან დაკავშირებული იმუნოსორბენტული ანალიზით (ELISA).

შედეგები: შრატის PGE2 მედიანური ინტერკვარტილური დიაპაზონი (IQR) უფრო ფართო დიაპაზონში მერყეობდა და მეტად იყო მომატებული ეპილეფსიის მქონე პაციენტებში 512 პგ/მლ (324.5-970.0) ჯანმრთელ კონტროლთან შედარებით 406 პგ/მლ (278.7-541.4), თუმცა,

მონაცემები მნიშვნელოვნად არ განსხვავდებოდა ეპილეფსიის დიაგნოზის მქონეთა ქვეჯგუფებში ($p>0.05$). ასევე, მხოლოდ პაციენტებში, რომლებიც იტარებდნენ მკურნალობას ვალპროატებით, PGE2 იყო შემცირებული , საშუალო IQR 490 pg/ml.

დასკვნები: ჩვენი შედეგები ემთხვევა პრეკლინიკურ მოდელებში წარმოჩენილ დასკვნებს, რომ ეპილეფსიის პერსონალიზებულ მედიცინაში ციტოკინები შესაძლოა განიხილებოდეს როგორც პოტენციური სამიზნე, მოლეკულურ საფუძველზე ფარმაკორეზისტენტულობის დასაძლევად, რაც წარმოადგენს მთავარ გამოწვევას ამჟამად ეპილეფსიის მართვასა და მკურნალობის გამოსავლის პრედიქციაში.