Original article

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Patients with generalised epilepsy have a higher white blood cell count than patients with focal epilepsy

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ABSTRACT – *Background*. Immunological alterations have been noted following seizures in the acute period, however little is known about the effect of type and severity of epilepsy on leukocyte count in the absence of seizures. *Methods*. We performed a retrospective chart review of adult epilepsy patients presenting for evaluation over a four-month period. Demographics, epilepsy type and characteristics, number and type of antiepileptic drugs, as well as medical co-morbidities were noted. *Results*. A total of 241 patients fulfilled study criteria. Variables correlating with leukocyte count were identified using univariate analysis. Based on multivariate analysis, only the correlation with type of epilepsy and use of more than two antiepileptic drugs remained statistically significant. Patients with generalised epilepsy had a higher leukocyte count (7.21 k/μL) compared to those with focal epilepsy (6.53 k/μL); the main difference was due to the number of monocytes. *Conclusion*. These findings raise the possibility that there are different neuro-immune profiles between patients with generalised and focal epilepsy.

Key words: immune, monocyte, leukocyte

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Alterations of the immune system of patients with epilepsy have been well documented in the literature (Billiau *et al*., 2005). The level of white blood cells (WBCs) is elevated in patients immediately after a generalised tonic-clonic or complex partial seizure (Shah *et al*., 2001) and even in the absence of seizure activity alterations in cytokine levels may be identified (Vezzani and Granata, 2005). However, an investigation into whether chronic changes in leukocyte levels are present in patients with different types or severities of epilepsy has never been performed.

The aim of the current study was to assess whether there is a correlation between the number or subtype of leukocytes and seizure frequency or type of epilepsy.

Table 1. Characteristics of study group (*n*=241).

Baseline demographics	
Age in years (Mean ±SD)	41.6 (±14.9)
Males	118 (49%)
Race	Caucasian: 202 (84%) African American: 28 (12%)
BMI (±SD)	29.1 (±7.6)
Obesity	160 (67%), 3 unavailable
Epilepsy Type	
Epilepsy type	Focal: 168 (70%) Generalised: 59 (24%) Unclassified: 14(6%)
Side (of focal epilepsy)	Bi-hemispheric: 14 (8%) Left: 68 (40%) Right: 59 (35%) Unclassified: 28 (17%)
Seizure Characteristics	
Seizure frequency per month (±SD)	9.4 (±22.7)
More than one seizure per month	118 (49%)
Age at seizure onset in years (±SD)	22.8 (±18.2)
Age at onset > 45 years	31 (13%)
History of GTC	155 (64%)
Last seizure > 6 months prior to evaluation	86 (36%)

Comorbidities	
Hypertensive	44 (18%)
Diabetic	14 (6%)
Smoker	52 (22%)
History of depression	74 (31%)
History of psychosis	19 (8%)
Epilepsy treatment	
Number of antiepileptic drugs (±SD)	2.0 (±0.9)
More than two antiepileptic drugs	71 (29%)
Vagal nerve stimulator	11 (5%)
Prior epilepsy surgery	22 (9%)
Imaging	
MRI (*n*=150)	Small vessel disease: 41 (27%)
MRI of focal epilepsy (*n*=138)	Mesial temporal sclerosis: 41 (30%)
PET (*n*=58)	Normal: 3 (5%) Unilobar: 18 (31%) Multilobar: 19 (33%) Diffuse: 18 (31%)
White blood cell count mean (±SD)	6.81 k/μL (±2.04)

BMI: body mass index; SD: standard deviation.

Methods

A retrospective chart review of patients with a diagnosis of epilepsy, admitted to the epilepsy monitoring unit or evaluated in the outpatient setting over a four-month period, was performed.

Only patients with a complete blood count and differential were included. Exclusion criteria included: age less than 18 years, recent infection, seizure on the day of presentation and intake of immuno-modulating drugs such as steroids or chemotherapeutic agents. Patients with an elevated WBC count were only included if an infection was ruled out.

Data collected included patients' demographics (age, gender, race, and presence of obesity defined as a BMI>30), epilepsy type (generalised, focal, or unclassified), side of focal epilepsy (bi-hemispheric, right, left, or unclassified), seizure characteristics (frequency per month, age at seizure onset, and history of generalised tonic-clonic seizures), comorbidities (hypertension, diabetes, smoking, history of depression, and history of psychosis), epilepsy treatment (number of antiepileptic drugs, antiepileptic drugs used, use of vagal nerve stimulator, and history of epilepsy surgery). The presence of findings suggestive of mesial temporal sclerosis on MRI was documented, as was the presence or absence of small vessel disease. The rationale for including this information was based on prior findings of lower rates of metastases in patients with lung cancer and small vessel disease, suggesting local alterations in immunity (Mazzone *et al*., 2009). PET findings were also graded as normal, unilobar, multilobar, or diffuse.

For statistics, the JMP 8.0 (SAS) software was used. ANOVA, Wilcoxon rank sum, and student's paired t-test were used depending on the variable analysed.

Using initial univariate analysis, variables with a more liberal significance level of 10% were identified and then tested in a multivariate linear regression model. Results were then considered statistically significant at the 5% level.

Results

Of the patients investigated, 241 fulfilled study criteria. The patients had a mean age of 41.6 years, 70% cases presented with focal epilepsy and the average number of antiepileptic drugs taken was two.

All patient characteristics are summarised in *table 1*. Using univariate analysis, the following variables correlated with the leukocyte count (*table 2*): obesity, age at onset greater than 45 years, use of more than two antiepileptic drugs, epilepsy type, side of focal epilepsy, and history of epilepsy surgery. Having more than one seizure per month (p=0.32) and having a seizure six months prior to evaluation (p=0.44) did not correlate with the leukocyte count.

In terms of specific antiepileptic medication used, only levetiracetam and phenobarbital correlated significantly with leukocyte count (*table 2*).

When the focal and generalised epilepsy groups were compared (*table 3*), the main difference between the groups was shown to be the monocyte count (0.70 for generalised epilepsy compared to 0.53 for focal epilepsy; p=0.022). More patients with generalised epilepsy than focal epilepsy also tended to take valproic acid (*table 4*). Using multivariate analysis, the difference in WBC count (p=0.04) and use of more than two antiepileptic drugs (AEDs) (p=0.04) between patients with focal and generalised epilepsy remained statistically significant.

The presence of small vessel disease or findings suggestive of mesial temporal sclerosis based on MRI, as well as PET abnormalities, did not correlate with the WBC count.

Discussion

Research on the role of the immune system in epilepsy is currently ongoing and has mainly focused on the acute postictal period. In a cohort of 22 patients with temporal lobe epilepsy, immediately following a seizure, Bauer *et al*. (2008) identified a transient increase in lymphocytes, neutrophils, and NK cells and a decrease in CD4 cells. These changes resolved by 24 hours. The same group (Bauer *et al*., 2009) was also able to identify postictal increases in interleukin 6, up to 24 hours following seizures, in a group of temporal lobe epilepsy patients. These changes were prominent in patients with right-sided seizures and absent in patients with mesial temporal sclerosis.

Studies evaluating chronic immune changes beyond the immediate postictal period are sparse. Eeg-Olofsson *et al*. (1988) showed that patients with focal epilepsy, compared to their relatives, had a lower level of immunoglobulin A and T4 lymphocytes, possibly due to the effect of anticonvulsants. Patients with both focal and generalised epilepsy also tended to have higher levels of autoantibodies (Peltola *et al*., 2000).

In our study population, we noted a correlation between leukocyte count and obesity, diabetes, and age. This has been previously reported in the literature (Ovbiagele *et al*., 2007) and was thus taken into account in order to analyse the potential impact of epilepsy variables on leukocyte numbers. In order to focus on the analysis of chronic interictal WBC counts, counts taken within a day of the last seizure were excluded.

Variables such as seizure frequency and side of epileptic activity were not found to be significant. We did, however, find a higher total leukocyte and monocyte count in patients with generalised epilepsy compared to focal epilepsy, even after controlling for the various types of antiepileptic medications. Moreover, this higher WBC count was present in patients with generalised epilepsy despite a greater use of valproic acid, a medication traditionally associated with leucopenia. This finding remained statistically significant after multivariate analysis and deserves further discussion. We also confirmed prior reports of decreased WBC counts associated with the use of epileptic drugs (Krause, 1988) and found that patients with more than two AEDs had lower counts.

Monocytes play a central role in the autoimmune pathological process underlying some inflammatory brain diseases such as multiple sclerosis, but their specific role in epilepsy, if any, remains to be elucidated. There is some data indicating a higher incidence of diabetes mellitus type I in patients with idiopathic generalised epilepsy (IGE), possibly implicating an autoimmune component involved in the pathogenesis of IGE (McCorry *et al*., 2006). Although our data may be consistent with such an altered immune mechanism, our results are preliminary and, as yet, insufficient to reasonably support such premature conclusions.

The current study raises the possibility that patients with IGE may have a different immune profile than those with focal epilepsy which cannot be attributed solely to the effect of anticonvulsants. One possible mechanism is that the interaction between the neural and immune mechanisms in these two patient populations is different. The hypothalamic-pituitary axis (HPA) is known to be affected by interictal and ictal discharges leading to a number of endocrine abnormalities (Pennell, 2009). This, in turn, may have a direct effect on the peripheral leukocyte count due to the close relationship between the HPA axis and immune

Table 2. Correlation between white blood cell count and variables, including AED intake, using univariate analysis ($p<0.10$).

	Mean WBC count (k/μL)	***p* value**
BMI		$p=0.0135$*
>30 (*n*=85)	7.25±2.35	
≤30 (*n*=153)	6.57±1.83	
Age at onset		$p=0.0236$*
>45 (*n*=31)	7.58±2.23	
≤45 (*n*=210)	6.69±2.00	
AED intake		$p=0.028$*
>2 (*n*=71)	6.26±1.74	
≤2 (*n*=170)	7.03±2.13	
Diabetes Mellitus		$p=0.034$*
Present (*n*=14)	7.93±2.86	
Absent (*n*=227)	6.73±1.98	
Prior epilepsy surgery		$p=0.0376$*
Yes (*n*=22)	5.84±1.65	
No (*n*=219)	6.89±2.07	
Epilepsy type (14 unclassified)		$p=0.022$*
Generalised epilepsy (*n*=59)	7.21±1.95	
Focal epilepsy (*n*=158)	6.53±1.95	
Side of focal epilepsy (28 unclassified)		$p=0.069$*
Left (*n*=57)	6.34±1.87	
Right (*n*=59)	7.01±2.30	
Bi-hemispheric (*n*=14)	5.86±1.24	
AED Intake		
Levetiracetam		$p=0.055$*
Yes (*n*=81)	6.45±1.82	
No (*n*=160)	6.99±2.14	
Lamotrigine		$p=0.25$
Yes (*n*=81)	7.02±2.02	
No (*n*=160)	6.70±2.06	
Phenytoin		$p=0.93$
Yes (*n*=36)	6.84±1.90	
No (*n*=205)	6.80±2.08	

Table 2. (*Continued*)

	Mean WBC count (k/μL)	*p* value
Carbamazepine		*p*=0.15
Yes (*n*=52)	6.44±2.19	
No (*n*=189)	6.90±2.00	
Phenobarbital		*p*=0.096*
Yes (*n*=10)	5.75±1.70	
No (*n*=231)	6.85±2.05	
Clonazepam		*p*=0.44
Yes (*n*=22)	7.13±2.65	
No (*n*=219)	6.77±1.98	
Pregabalin		*p*=0.99
Yes (*n*=32)	6.80±1.69	
No (*n*=209)	6.81±2.10	
Oxcarbazepine		*p*=0.42
Yes (*n*=35)	6.54±1.99	
No (*n*=206)	6.85±2.06	
Topiramate		*p*=0.84
Yes (*n*=56)	6.85±1.87	
No (*n*=184)	6.79±2.10	
Valproic Acid		*p*=0.41
Yes (*n*=38)	6.55±2.08	
No (*n*=203)	6.85±2.04	
Zonisamide		*p*=0.46
Yes (*n*=20)	6.48±1.67	
No (*n*=221)	6.83±2.08	
Gabapentin		*p*=0.64
Yes (*n*=13)	6.54±1.81	
No (*n*=228)	6.82±2.06	
Felbamate		*p*=0.41
Yes (*n*=7)	6.17±1.41	
No (*n*=234)	6.82±2.06	

AED: antiepileptic drugs; *$p<0.10$.

Table 3. White blood cell subtypes in focal *vs*. generalised epilepsy.

	WBC (k/μL)	Neutrophils (k/μL)	Lymphocytes (k/μL)	Monocytes (k/μL)	Eosinophils (k/μL)	Basophils (k/μL)
Generalised epilepsy	7.21	4.14	2.29	0.70	0.18	0.03
Focal epilepsy	6.53	3.71	2.10	0.53	0.16	0.04
p value	0.022*	0.066	0.08	0.022*	0.67	0.56

WBC: white blood cell count.

Table 4. AED intake based on diagnosis.

AED	Focal Epilepsy *n*=168	Generalised Epilepsy *n*=59	Unclassified *n*=14	*p* value
Levetiracetam	61	16	4	0.39
Lamotrigine	57	21	3	0.57
Phenytoin	28	7	1	0.44
Carbamazepine	38	10	4	0.53
Phenobarbital	8	2	0	0.49
Clonazepam	15	5	2	0.8
Pregabalin	26	5	1	0.28
Oxcarbazepine	31	3	1	0.018*
Topiramate	31	15	4	0.77
Valproic Acid	17	19	2	0.0008*
Zonisamide	16	4	0	0.23
Gabapentin	9	3	1	0.96
Felbamate	6	1	0	0.49

*$p<0.05$

modulation. As such, differences in the "central" neuronal networks interacting with the HPA axis in patients with IGE versus focal epilepsy may translate into "peripherally" different immune profiles.

On the other hand, the immune system is postulated to play an active role in the pathogenesis of epilepsy due to blood brain barrier disruption, as a result of systemic inflammation. In one animal model, antagonising inflammation has been shown to reduce the severity of status epilepticus (Marchi *et al*., 2009). It is conceivable then that in such a model where chronic low grade inflammation contributes to the generation of seizures, patients with focal epilepsy, and as such, focal brain pathology, have a lower "inflammatory" threshold, requiring fewer WBCs. Further research is required to confirm these hypotheses. □

Disclosures.
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