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Biochemical and haematological parameter changes in patients taking anti-epileptic therapy

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Abstract
Introduction and Background: Epilepsy is a brain ailment that causes epileptic seizures due to the neurobiological, cognitive, psychological, and social effects of the condition. The study aimed to analyse alterations in biochemical and haematological parameters in patients undergoing anti-epileptic therapy.
Material and Methods: This study was a cross-sectional observational study undertaken with compliance at the Madha Medical College and Research Institute, Chennai, Tamilnadu between January 2015 to January 2016. Prior to enrollment, all study participants provided informed and written consent. Patients diagnosed with epilepsy who were prescribed antiepileptic drugs were included in the study at the Neurology outpatient department.
Results: Haematological and biochemical markers were assessed once during the enrollment process. 23.93% of patients with epilepsy experienced a drop in haemoglobin levels with a mean of 10.19. Females showed a notable decrease in Hb levels compared to males, while patients on AED polytherapy had a significant drop compared to those on monotherapy. Female patients who had AED polytherapy were at a higher risk of developing anaemia. Approximately 9.41% of individuals with epilepsy saw a reduction in white blood cell levels, while 3.92% experienced a decrease in platelet count, with mean values of 2570 U/L and 101900.25 U/L, respectively. There was no statistically significant variation in WBC and Platelet levels between genders or between patients on AED monotherapy and polytherapy.
Conclusion: Therefore, patients undergoing AED polytherapy should ideally have their haematological and biochemical markers monitored regularly throughout treatment.

Keywords: Biochemical, hematological parameters, anti-epileptic therapy

Introduction
Epilepsy is a brain ailment that causes epileptic seizures due to the neurobiological, cognitive, psychological, and social effects of this condition. Antiepileptic medications (AEDs) are commonly prescribed for various illnesses such as epilepsy, movement or cognitive impairments, and neutropenic pain. 70% of epileptic patients achieve seizure freedom with a single medicine with careful drug administration and dosage adjustments. Evaluating the treatment of epilepsy typically relies on using a single therapy [1-3].

The usage of multiple AEDs may lead to negative effects in patients. Reported side effects include weight gain, metabolic acidosis, nephrolithiasis, angle closure glaucoma, skin rash, hepatotoxicity, colitis, as well as movement and behavioural abnormalities. Various adverse effects have been reported in patients taking antiepileptic drugs, such as hypochromic anaemia, eosinophilic leukemoid reaction, and exfoliative dermatitis, cross hypersensitivity syndrome, neutropenia, pure red cell aplasia, and hypersensitivity syndrome [4, 5]. Common adverse effects of antiepileptic drugs include dizziness, drowsiness, mental impairment, and hematologic side effects such as purpura, anaemia, thrombocytopenia, lymphadenopathy, elevated white blood cell count, lymphocytosis, non-Hodgkin's lymphoma, and prolonged bleeding time. Additional adverse effects may involve agranulocytosis, aplastic anaemia, leukopenia, and thrombocytopenia [4-6].

Traditional AEDs are frequently utilised as initial medications and are linked to a broad spectrum of negative effects. Newer AED monotherapy is known to have fewer side effects, but AED polytherapy can lead to adverse consequences because to interactions caused by varying kinetic profiles. Patients with epilepsy may have metabolic side effects while undergoing therapy with antiepileptic drugs. These impacts can be subtle and insidious, taking many years to become clinically evident and have a detrimental impact on overall health. Regular monitoring of blood tests is not yet advised in clinical practice for people with epilepsy. This study aimed to investigate the impact of AEDs on haematological and biochemical markers and compare the effects of AED monotherapy and polytherapy in people

with epilepsy at a specific tertiary care institution [5-7].

Phenobarbital, carbamazepine, phenytoin, and valproic acid exhibit drawbacks including low response rates, significant side effects, many medication interactions, and a narrow therapeutic range. Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and zonisamide have enhanced acceptability profiles, limited potential for interactions, and notably reduced enzyme-inducing or inhibitory effects [6-8].

Monotherapy is the preferred treatment for epilepsy due to its ability to minimise adverse effects and drug interactions. Some people may obtain seizure control with low dosages of a single medication, while others may require higher doses to achieve better results without experiencing adverse effects. Rational polypharmacy targets many receptors or ion channels to enhance inhibition and decrease excitation concurrently. Interactions among antiepileptic drugs are influenced by their kinetics and clearance rate from the liver, which might affect their effectiveness and potential side effects [7-9].

Materials and Methods

This study was a cross-sectional observational study undertaken with compliance at the Madha Medical College and Research Institute, Chennai, Tamil Nadu between January 2015 to January 2016. Prior to enrollment, all study participants provided informed and written consent. Patients diagnosed with epilepsy who were prescribed antiepileptic drugs were included in the study at the Neurology outpatient department.

Statistical Analysis: Data were calculated and statistical analysis was performed using SPSS version 18. Descriptive statistics, such as mean and frequencies, were utilised to summarise the data. Inferential tests, including the Chi-square test, were employed to compare categorical variables between groups. A two-sided test was regarded statistically significant.

Results

During the study period, 200 individuals with psychogenic non-epileptic seizures (PWE) were included, consisting of 120 males and 80 females aged between 18 and 65 years. Out of 200 participants, 13 reported a history of smoking and 34 had a family history of epilepsy.

Table 1: Usage pattern of anti-epileptic drugs in people with epilepsy (N=200)

Sr. No.	Type of AED	Patients	%
1.	Monotherapy	100	50%
2.	Conventional + newer AEDs	60	30%
3.	Newer AED combination	30	15%
4.	Conventional AED combination	10	5%
Total		200	100%

There were 120 cases of focal seizures, 40 cases of generalized seizures, and 15 cases that were unclassified. In monotherapy, 100 participants used AEDs, while in polytherapy with two or more AEDs, 60, 30, and 10 participants used them accordingly (Table 1).

Table 2: Adverse drug reactions with antiepileptic drugs

ADRs and the affected system	PWE count with ADR	PWE Separately	PWE regarding polytherapy
Central nervous System			
speech slurred, migraine, parasthesia, and diplopia	20	12	25
Bone related			
Back ache, joint pain, and knee pain	12	05	08
Others			
Acne, indigestion, appetite loss, and weight gain	05	02	02

The ADR profile indicated that 25 adverse events were connected to bone, 57 to the central nervous system, and 9 to other areas (Table 2).

Haematological and biochemical markers were recorded once at the time of enrollment. 23.93% of patients with epilepsy experienced a drop in haemoglobin levels with a mean value of 10.19. Females showed a notable decrease in Hb levels compared to males, and patients on AED polytherapy had lower Hb levels compared to those on monotherapy. Female patients who had AED polytherapy were at a higher risk of developing anaemia.

Approximately 9.41% of individuals with epilepsy saw a reduction in white blood cell levels, while 3.92% reported a decrease in platelet count, with mean values of 2570 U/L and 101900.25 U/L, respectively. There was no statistically significant variation in WBC and Platelet levels between genders or between patients receiving AED monotherapy and polytherapy. Calcium levels declined in 4.70% of individuals with a mean of 7.38 mg/dl, while phosphorous levels decreased in 3.13% with a mean value of 1.76 mg/dl. There was no statistically significant variation in calcium and phosphorus levels between genders or between individuals receiving AED monotherapy and polytherapy.

Discussions

Using AEDs in people with epilepsy to achieve optimal seizure control while minimizing adverse drug reactions is difficult. Seventy percent of people with epilepsy can achieve effective seizure control with a single antiepileptic drug if the drug is chosen correctly. Approximately 20-30% of cases of epilepsy necessitate the use of two or three antiepileptic drugs simultaneously. Polytherapy may necessitate vigilant monitoring for adverse drug reactions. The study results showed that most people with epilepsy were in a younger age range, with a higher number of men affected [9-11].

Polytherapy with antiepileptic drugs was used, and partial seizures occurred more frequently than generalized seizures. Our study's haematological and biochemical analysis showed a decrease in levels of haemoglobin, white blood cells, platelets, calcium, and phosphorus, along with an increase in alkaline phosphatase levels in individuals with epilepsy. Female patients and patients taking AED polytherapy experienced a notable decrease in Hb levels. Folate is vital and necessary for rapid division of cells and tissues like bone marrow.8 Antiepileptic medications exhibit anti-folic acid activity, potentially leading to bone marrow suppression and causing blood disorders such as aplastic anaemia, leukocytopenia, and thrombocytopenia. Although folic acid itself is not biologically active, its significance lies in its conversion to dihydrofolic acid in the liver by the reductase enzyme, leading to the production of tetrahydrofolate and other important derivatives [12-14].

AP is regarded as an indicator of the robustness of hepatocytes. Serum alkaline phosphatase levels may rise in conditions with heightened osteoblastic activity, hepatobiliary illnesses with intra or extra hepatic cholestasis, as well as in sepsis, chronic inflammatory bowel disease, and thyrotoxicosis. The rise in enzyme activity in three patients may be due to liver injury affecting hepatocyte integrity caused by valproic acid or interactions in pharmacokinetics of antiepileptic drugs. Previous studies have indicated that topiramate should be used carefully in patients with liver impairment due to the potential decrease in clearance [15-17]. A further investigation shown that alterations in serum biochemistry, signalling a susceptibility to developing rickets or osteomalacia, manifest within 90 days after initiating treatment with either carbamazepine or valproic acid as the only therapy. Lymphocytosis, a medical disorder characterized by increased lymphocytes, has been observed in seven patients undergoing polypharmacy with AEDs, where the lymph count exceeds 40% [18, 19]. An elevated level of lymph concentration typically indicates acute illnesses like Epstein Barr virus infection, viral hepatitis, leukaemia, bone marrow malignancy, or radiation therapy. The study suggests that changes in patients could be linked to alterations in bone marrow density caused by pharmacokinetic interactions. Leukopenia is a reduction in white blood cell count, which are cells that fight diseases. Leukopenia can be caused by chemotherapy, radiation therapy, or immune system diseases. A low white blood cell count in this study could be associated with prolonged usage of many antiepileptic drugs. Published reports suggested a likely connection between the drug interaction and blood disorder while undergoing lamotrigine/phenobarbital treatment [20-22].

AEDs block this reductase enzyme, causing anaemia, leukocytopenia, and thrombocytopenia. Research indicates that fluctuations in haematological factors like haemoglobin levels during a 12-month period are linked to a decreased likelihood of experiencing illness and death later on, regardless of initial anaemia and other key factors.10 A substantial difference in ALP levels was seen between monotherapy and polytherapy, with polytherapy showing a stronger impact on ALP levels. ALP is recognised as a marker for hepatocellular activity. An elevation in ALP levels may result from an increase in osteoblastic activity [23-25]. A significant number of patients undergoing AED polytherapy showed changes in haematological and biochemical markers. Over 55% of patients were observed to be using polytherapy, defined as receiving two or more antiepileptic drugs. Thus, AED combination therapy is expected to cause notable alterations in Hb and ALP levels, resulting in adverse effects. No significant changes were observed in other measures such as WBC, platelet, calcium, and phosphorus. Additional research is needed to explore these findings in specific patient cohorts, particularly individuals with epilepsy who are receiving multiple antiepileptic drugs, and in a broader sample size [26-28].

Conclusion

In an epileptic population, polytherapy with AEDs may lead to pharmacokinetic and pharmacodynamic interactions. Patients who do not adhere to their prescription should be monitored for therapeutic levels, and ineffective AEDs should be removed cautiously. This study is limited by the absence of follow-up, inconsistent data, and a small sample size. This study demonstrated notable changes in the levels of haemoglobin (Hb) and alkaline phosphatase (ALP) after using antiepileptic drug (AED) polytherapy in people with epilepsy (PWE). It is wise to regularly check haematological and biochemical markers in individuals undergoing AED polytherapy treatment.

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None

Conflict of Interest

None

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