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Effects of Antiepileptic Drug (Valporic Acid) on Complete Blood Count Parameters among Patients Attending Eltigain Elmahi Neurological and Psychological Hospital-Khartoum Stata -Sudan.

A thesis submitted in Partial fulfillment for the Requirement of the Master Degree in Haematology

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Dedication

To my parents……..reason of existence

To my siblings……..joy of life

To my friends……...treasure of life

Acknowledgment

Thanks to ALLAH for giving me strength to achieve this research though a tough community base, which reminded me to be grateful of having well fair and full appreciation to that.

Thanks to Dr. Hussam for guiding and enlightening though the path of this work

Thanks to who worked behind sense and never get enough thanks……..

Thanks to everyone who did not got mentioned, not intentionally

Abstract

Background

Epilepsy, affecting 5-10 per 1000 population, is characterized by the occurrence of at least two unprovoked seizures brought about by abnormal discharge of cortical neurons. The lifetime risk of developing psychiatric disorder with epilepsy is extremely high with such individuals having greater psychiatric co-morbidity when compared to the general population. Valporic acid is a drug used as mood stabilizer and ant convulsion episodes, it has been given indifferent doses prescribed by the physician and most of time as anti-psychological drugs used for life, some side effects occur. So this study aim to focus on the side effects that may present among complete blood count parameters, such as red blood cell count, hemoglobin concentration, total whit blood count and related differential count of Neutrophil, Lymphocyte, and Monocyte. Beside Platelet count and related indices.

Method

Descriptive – cross sectional study conducted among 91 psychotic patients with epileptic episodes, set as case group and healthy individuals with no signs of anemia or infection set as control group to compare data with case group. Blood samples were collected in Ethylene Diamin Tetra Acetic Acid (EDTA) for complete blood count CBC, using automatic hematology analyzer Sysmex KX 21.

Result

Complete blood count parameters of case group and control group when compared with each other, revealed that significant difference (p value $\leq$ 0.05) in RBC, Hb and PCV as they were increased among case group than control group (the means of RBCs were $4.78\pm0.49\times 10^{6}\ /cmm$, $4.44\pm060\times$

10^6 $/cmm$ and Hb 13.29±1.78g/dl, 12.68±2.14g/dl and PCV 42.38± 5.45%, 38.28±6.92%), while platelet count was decreased among case group than control (mean ± SD = 208.09± 100.99× 10^3 $/cmm$, 275.12±101.70× 10^3 $/cmm$).

group (p value ≤ 0.05), with difference (p value ≤ 0.05) obtained through independent T test. Dose of drug and duration of taking did not give significant difference (p value > 0.05).

Conclusion

Anti-epileptic drug, valporic acid has an effect on some of complete blood count parameters, such as platelet count, regardless the duration of medication and gender of patients.

ملخص الدراسة:

المقدمة :

الصرع يؤثر علي 5—10من السكان لكل الف من السكان ويتميز بحدوث نوبتين علي الأقل والذي ينتج من التفريق غير الطبيعي للخلايا العصبية القشرية ومع مرور الزمن يتطور الخطر إلي إضطرابات نفسية مع الصرع ويصل اقصي لإرتفاع مع الأشخاص ذوي الامراض النفسية مقارنة بعامة السكان حمض الفالبوريك يستخدم كعلاج لإستقرار المزاج ومضاد لنوبات التشنج ويستخدم بجرعات مختلفة بوصفة من الأطباء ، في معظم الاحيان هي مضادة للامراض النفسية لكن لديها بعض الآثار الجانبية لذا هذه الدراسة تهدف علي التركيز وعلي الآثار الجانبية التي نجدها في قياس الدم الكامل مثل تعداد خلايا الدم الحمراء وتركيز الهيموغولبين والعدد الكلي لخلايا الدم البيضاء وتكون مصحوبة وبتعداد تمايز الخلايا البيضاء مثل الخلايا العدلة والليمفاوية والأحادية بجانب تعداد الصفائح الدموية ومعاملاتها .

المنهجية:

هذه الدراسة مقطعية وصفية أجريت بين (91) مريض نفسي مصحوبة بنوبات صرع والدراسة مقارنة بين مجموعتين مجموعة حالات مرضية, ومجموعة الأصحاء (المجموعة الضابطة) ليست لديهم أي اعراض أنيميا أو عدوي ، اخذت عينة دم في مضاد التجلط أديتا لكلا المجموعتين لعمل تعداد الدم الكامل بإستخدام جهاز تحليل الدم الكامل الأوتوماتيكي (سيسمكس)

النتائج:

عند مقارنة تعداد الدم الكامل لمجموعة المرضي والمجموعة الضابطة وجد أن هنالك إختلاف معنوي بين المجموعتين أي ان القيمة المعنوية اكثر من (0.05) في خلايا الدم الحمراء والهيموغولبين والهيماتوكريت كزيادة في مجموعة المرضي مقارنة بالمجموعة الضابطة ومتوسط خلايا الدم الحمراء كانت (4.78±0.49×10 6 /سم 3 ، 4.44± 060×10 6 سم3) والهيموغوولوبين (13.29±1.78 جرام/ديسيلتر ، 12.68±2.14 جرام/ديسيلتر) الهيماتوكريت (42.38±5.45% ، 38.28±6.92%) بينما الصفائح الدموية كانت اقل حول مجموعة المرضي مقارنة بالمجموعة الضابطة المتوسط (208.59±100.99×10 3 خلية في المليمتر ، 275.120±101.7×10 3 خلية في الميليمتر).

والإختلاف في القيمة المعنوية أو وجود نفرق في القيمة المعنوية أجريت خلال عمل إختبار (T) المستقل وجرعة الدواء وفترة أخذ الجرعة لم تعطي فرقاً كبيراً أو إختلافاً منعوياً .

الخاتمة:

الادوية المضادة للصرع وحامض الفالبوريك له تاثير علي بعض قياسات الدم ومعلمات الدم مكثل الصفائح الدموية وذلك تبعاً لمدة العلاج ونوع المرضي .

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List of Abbreviation

AA	Arachidonic Acid
Abbreviation	refer to
BDNF	Brain-derived Neurotrophic Factor
CBC	Complete blood count
EDTA	Ethylene Diamin Tetra Acetic Acid
GABA	Y-aminobutyric Acid
GDNF	Glial-Derived Neurotrophic Factor
Hb	Hemoglobin
L%	Lymphocyte %
M%	Monocyte %
MCH	Mean Cell Volume
MCHC	Mean Cell Hemoglobin Concentration
MPC	Mean Platlet Component Concentratin
MPV	MeanPlatlet Volume
N%	Neutrophil %
PCV	Packed Cell Volume
PDW	Platlet Distribution Width
P-LCR	Platlet Large Cell Ratio
RDW-CV	Red Distribution Width-co-efficient
TLE	Temporal lobe Epilepsy
TWBC	Total White Blood Cell Count
VEGF	Vascular Endothelial Growth Factor
VPA	Valporic Acid

Chapter 1

Introduction and literature review

1-1 Introduction

1-1-1 Epilepsy

Epilepsy, affecting 5-10 per 1000 population,[1] is characterized by the occurrence of at least two unprovoked seizures brought about by abnormal discharge of cortical neurons. The lifetime risk of developing psychiatric disorder with epilepsy is extremely high with such individuals having greater psychiatric co-morbidity when compared to the general population, neurological controls and individuals with a chronic non-neurological condition. [2] Psychiatric co-morbidity is estimated to be between 20°/o-30°/o [3] within a community setting, however in specialized treatment settings, these rates are even more pronounced, eg. Neurology/neuropsychiatry clinics where rates up to 50% are not uncommon. [4] Temporal lobe epilepsy (TLE) is a sub-type of epilepsy renowned for higher rates of psychiatric illness and rates between 50%-70% are common. [5,6] It is postulated that these higher rates arise due to deficits in the temporal lobe structures that comprise the limbic system and impact on emotional processing and regulation [7]. Depression affects a significant proportion of individuals with TLE; up to 30% [8-9] Anxiety disorders are a close second with rates up to 25%. Psychosis is another entity that is more common in TLE with the association between the temporal lobe and psychosis only being made in the last century. This was initially reported by Slater & Beard [10] in 1963 while Flor Henry [11].

Subsequently noted the similar clinical phenotypes of TLE with psychosis and schizophrenia in1969. The prevalence of psychoses in TLE is estimated to be between 5%-10% which is ten times higher than that seen in the general population and in certain settings this figure is more substantial [12]. Psychoses generally tend to manifest approximately 5-12 years after an

epileptic disorder is diagnosed [13] with the postictal psychoses being by far the most common [14]. The psychoses associated with TLE are generally regarded not to improve with epilepsy surgery and thus such candidates are generally excluded from surgical intervention. However patients with co-morbid schizophrenia need not necessarily be deprived of surgical treatment as they benefit from such therapy [15].

1-1-2Antiepileptic drug

Valporic acid (VPA) is a medication primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches[16]. Valproate is effective in rapid cycling and mixed episode bipolar disorder than lithium [17]. It also has superior efficacy than lithium in treating schizoaffective disorders and augmentation therapy for schizophrenic patients not adequately responded to antipsychotic medications . It is useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures. It can be given intravenously or by mouth. Long acting formulations exist [18-19]. The Depakote form of valproic acid is approved for the acute phase of bipolar disorder.

It is also commonly used on a long-term basis, although its prophylactic effects have not been as well established. Valproate is used as a first-line treatment for bipolar disorders especially for patients with rapid cycling and mixed episodes, as well as in combination with lithium for patient‘s refractory to lithium monotherapy. Oral loading can lead to rapid stabilization, and plasma levels must be monitored to keep drug levels within the therapeutic range [20-21]. Common side effects include gastrointestinal (GI) distress, tremor, sedation, hair loss, increased appetite, and weight gain. Hepatic failure, pancreatitis and hyperammonemic encephalopathy are rare serious side effects associated with use of valproate.

It is known to cause serious abnormalities in the baby if taken during pregnancy. Because of this it is not typically recommended in women of childbearing age. Menstrual disturbances, polycystic ovaries, hyperandrogenism, obesity, and insulin resistance may also be associated with valproic acid therapy [22]. Overdose with valproate can result in heart block, coma, and death. Hemodialysis may be useful in clearing the drug rapidly, and naloxone may reverse the central nervous system depressant effects [23].

1-1-3Mechanism of Action of Valproate

The specific biochemical mechanism of valproate action in stabilizing mood is unknown. Its anticonvulsant effects are rapid in onset, while antimanic and antidepressant effects are slower in onset which requires chronic administration. It exerts effects by modulation of dopaminergic and serotonergic neurotransmitters, antagonism of glutamate NMDA activity , enhancement of brain γ-aminobutyric acid (GABA) synthesis and degradation, and blockage of voltage sensitive Na+ channels, alter intracellular signaling through actions on second messenger systems secondary messenger systems, modulate extra hypothalamic neuropeptides. In additions it has neuroprotective effects which increase the levels of neuroprotective proteins through suppression of an up regulated brain arachidonic acid (AA) cascade, which can cause cell damage and behavioral changes [24-25]. GABA neurotransmission: GABA is an inhibitory neurotransmitter that plays an important role in regulating dopamine and glutamate neurotransmission. It was found that patients with bipolar disorder had lower GABA levels, which results in excitotoxicity and can cause apoptosis (cell loss) . In general the mechanism of action of valproate is complex and still the subject of uncertainty. The drug appears to act by

enhancing GABAergic function. Thus it increases GABA release, inhibits catabolism and increases the density of GABA-B receptors in the brain. There is also evidence that it increases the sensitivity of GABA receptors to the action of the inhibitory transmitter. Other actions that may contribute to its therapeutic effects include a decrease in dopamine turnover, a decrease in the activity of the NMDA-glutamate receptors and also a decrease in the concentration of somatostatin in the CSF. Valpraote produce its manic effect through this GABAergic effect where sodium valproate raises cerebral and cerebellar levels of the inhibitory synaptic neurotransmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase, succinate-semialdehyde dehydrogenase and by inhibiting the re- uptake of GABA by neuronal cells . Reduction in phosphatidylinositol: The other mechanism where valproate boost its effect is through protection against a seizure-induced reduction in phosphatidylinositol [26-28] triphosphate (PIP3) [29]. Histone deacetylase-inhibiting effect: Valproate also has histone deacetylase- inhibiting effects where valpraote shows it neuropretive effects. This neuroprotective effects which increase the levels of neuroprotective proteins through suppression of an up regulated brain arachidonic acid (AA) cascade, which can cause cell damage and behavioral changes. Intermediate molecules mediating these effects include vascular endothelial growth factor (VEGF, neuroprotective brain-derived neurotrophic factor (BDNF) and Glial-derived neurotrophic factor (GDNF) [30-31].

1-1-4 Complete blood count parameters

The values of the complete blood count (CBC) parameters can vary according to numerous pre-analytical, analytical, pathological and physiological factors such as age, sex, height, environment, race,

nutritional state, ethnic origin, lifestyle, biorhythms, and consumption of tobacco, alcohol or medicine [32]. Circulating blood cells, including red blood cells (RBCs), white blood cells (WBCs), and platelets, are counted and sized electronically by modern instruments [33-34]. One such instrument, generates an electrical pulse when a blood cell passes through a small aperture surrounded by electrodes. Each electrical pulse represents an individual cell, and the pulse height indicates the cell volume. Therefore, the electronic counter not only registers the total cell count but also estimates the average cell volume and the variation in cell size. In the context of RBCs, for example, these measurements are referred to as the mean corpuscular volume (MCV) and the RBC distribution width, respectively. Modern electronic counters are also capable of multimodal assessment of cell size and content, thus providing additional information about the various categories of WBCs including neutrophils, lymphocytes, monocytes, eosinophils, and basophils (ie, 5-part differential). Two other ―measured variables‖ of the complete blood cell count (CBC) are hemoglobin (Hb) and hematocrit (Hct). Both provide equivalent information, approximately conveyed by the RBC count, and are interchangeable [35-36].

The Hb is computed by a spectrophotometer after RBCs are lysed in a given volume of blood and the Hb is chemically converted into a stable pigment. The Hct represents the percentage of a given volume of whole blood that is occupied by packed RBCs [37-38]. For practical purposes, the variables to focus on when examining the CBC are Hb (as a general indicator of anemia or polycythemia), MCV (a key parameter for the classification of anemias), RBC distribution width (a relatively useful parameter in the differential diagnosis of anemia), RBC count (an increased RBC count associated with

anemia is characteristic in the thalassemia trait), platelet count (to detect either thrombocytopenia or thrombocytosis), and WBC count with differential (usually gives important clues for the diagnosis of acute leukemia and chronic lymphoid or myeloid disorders as well as for the presence of leukopenia and neutropenia) [39]. Prediction of the hematological changes enables the clinician to establish an effective and early therapeutic intervention in order to prevent the occurrence of major complications. These parameters are measurable indices of blood that serve as a marker for disease diagnosis [40]. Abnormalities such as anemia and thrombocytopenia have been observed in patients with malaria [41].

2-1 Rational

Epilepsy is one of the neuropsychiatric disorders, it is known of convulsion episodes, which can occur any time if it is not controlled, patient will always be on medication and with time many physiological changes happened and they wouldn‘t be bound to specific reason and also can‘t be neglected. So this study aimed to evaluate the effects of antiepileptic drug (valporic acid) which is drug of choice on complete blood count in epileptic patients under treatment and therefore predicted damage can be avoided.

3-1 Objectives

1.3.2 General Objectives

To assess effects of antiepileptic drug (valporic acid) on Hematological parameters among Sudanese with epileptic episodes.

1.3.2 Specific Objectives

- To measure the RBCs and RBCs indices count in cases and control.
- To measure the WBCs count in cases and control.
- To measure the PLTs count in cases and control.
- To correlate changes of parameters with age, gender and duration of treatment with valporic acid

Chapter Tow

Literature Review

2-1 Literature Review

Epilepsy can be defined as a chronic neurologic condition comprising different syndromes and diseases characterized by recurrent unprovoked seizures and recurrent clinical events or epileptic seizures, which occur in the absence of a metabolic or toxic disease or fever. According to WHO, epilepsy is one of the most common neurological disorders affecting approximately 50 million people [(42)].

Previous study described that during the course of a prospective serial study over a period of one year, findings compatible with immune-mediated thrombocytolysis accompanied the administration of valproic acid in about half of 45 children with epilepsy. Thrombocytopenia occurred in 15 and neutropenia in 12 patients, but was transient and self-limiting in each [43]. Other study showed Seventeen (17.7%) patients in group treatmented with valporic acid developed thrombocytopenia, compared with two (4.2%) in the comparison group ($P<0.05$). The platelet count was negatively correlated to serum valproic acid level and age, and positively correlated to polytherapy. The duration of valproic acid treatment was not a confounding factor in the age-related decrease in platelet count [44]. Also other study revealed that a total of 851 VPA levels and concomitant platelet counts were analyzed in 265 patients. Of these, 17.7% of patients experienced at least one episode of thrombocytopenia (platelet count $\leq$100,000/μl) after exposure to divalproex sodium. A significant negative correlation was found between VPA levels and platelet counts. Women were significantly more likely to develop thrombocytopenia [45].

2-2 Epidemiology of epilepsy

Epilepsy is the commonest neurological condition affecting people of all ages, race and social class. There are an estimated 50 million people with epilepsy in the world, of whom up to 75% live in resource-poor countries with little or no access to medical services or treatment [46,47] .

Study demonstrated in the Rochester which followed a population over a 50-year period. The incidence of a first unprovoked seizure was 61 per 100,000 compared to the incidence of epilepsy of 44 per 100,000 [48]. Overall, while difficult to confirm, the incidence of first single unprovoked seizures is likely to lie somewhere in the range of 50 and 70 per 100,000 in

industrialised countries but may be much higher in developing countries [49]. Studies have shown prevalence rates for active epilepsy in developed countries of between 4 and 10 per 1000(50), although most studies give a prevalence rate of active epilepsy of 4−7per 1000.In systematic review [51].

2-2-3 Etiology of epilepsy

2-2-3-1 Heredity and eugenics

According to eugenic theory, epilepsy was inherited by Mendelian mechanisms, usually in a recessive manner, and by either positive or negative eugenic practices could potentially be removed (or at least minimized) from a population [52].

2-2-3-2 Psychological theories of causation of epilepsy

Among patients and their physicians it had been long held that epilepsy may be due to psychological causes—notably stress, psychic trauma, and shock. Exactly how ‗‗stress‘‘causes epilepsy though has remained obscure, and many theories, some fanciful, have been propounded [53].

2-2-3-3 Autointoxication causing epilepsy

According to this theory, epileptic seizures were caused by toxins produced within the person‘s own body (not dissimilar to Galen‘s theory of humours and Reynold‘s eccentric epilepsy‘‘). Most believed that these toxins arose in the bowel, either through fermentation or from bacteria [54].

2-3 Classification of epilepsy

The new classification has both a basic and expanded version, depending upon the needs and expertise of the individual utilizing the classification. The basic version

is a contracted form of the expanded version. Seizures are defined by onset as: focal, generalized, unknown, or unclassifiable. Focal is synonymous with the old term partial. The term generalized has been retained unchanged. A generalized onset seizure is when both hemispheres (potentially asymmetrically) are activated at onset of the seizure, according to behavior and EEG. Unknown onset refers to when the onset is unknown but other manifestations are known.[55] This is clarified further below. Unclassified remains as a category, although usage may decrease given the addition of additional seizure types and the unknown onset category. Few events are clearly seizures, yet unclassifiable Focal seizures optionally are classified as aware or impaired awareness seizures. These terms map to the former terms simple‖ and complex, respectively. Impaired awareness and loss of consciousness are not synonymous. If awareness in impaired at any time during a focal seizure, impaired awareness should be included. This is an exception to the rule of first , where the first sign or symptom defines the seizure type, even if more prominent features occur later [56].

If awareness is unknown, then this level of classification should be omitted when classifying the seizure type. In the basic classification, the next step after consideration of the level of awareness for a focal seizure entails defining the onset as motor or non-motor. The expanded classification includes subdivisions with more granularities. Secondarily generalized seizures are now called focal to bilateral tonic-clonic seizures, in order to restrict generalized to seizures of generalized onset. When classifying generalized seizures aware vs. impaired awareness is omitted, since awareness is impaired in most generalized seizures. The motor or non-motor (absence) designation is used as well. Generalized motor seizures

can further be classified as tonicclonic or other motor. Unknown onset seizures can also be classified as tonic-clonic or other motor [57].

Any name can omit unambiguous words, such as focal tonic, instead of focal motor tonic. Caution is advised in the use of tonic-clonic, as this term has a specific definition and should not be used as a wastebasket term for all motor activity. The word onset can also be omitted where its meaning is implied.

The nature of seizure onset is crucial, and a seizure whose onset was un witnessed, followed by tonic-clonic activity should be labeled an unknown onset to bilateral tonic-clonic seizure. The level of confidence for declaring a focal or generalized onset is somewhat arbitrarily set to 80% confidence (paralleling the usual permissible false negative rate in clinical statistics) [58].

2-4 Pathophysiology of epilepsy

Seizures are paroxysmal manifestations of the cerebral cortex.

A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates From the grey matter of any cortical or subcortical area (18).Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and excess excitability spread either locally to produce a focal seizure or more widely to Produce a generalized seizure. This onset propagates by physiologic pathways to involve adjacent to remote areas. As an abnormality of potassium conductance, a defect in the voltage activated ion channels, or a deficiency in the membrane ATPase linked to ion transport may cause neuronal membrane unstable and cause a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotrophin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas a-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation. During a seizure, the demand for blood flow to the brain increases to carry off CO2and to bring substrate for metabolic activity of the neurons, as the seizure prolongs, the brain suffers more from ischemia that may result in neuronal destruction and brain damage. Mutation in several genes may be linked to some types of epilepsy. Genes that code for protein subunits of voltage- sensitive and ligand-activated ion channels have been associated with the generalized epilepsy and infantile seizure syndromes. One speculated mechanism for some forms of inherited epilepsy are mutation of the genes which code for sodium

channel proteins these defective sodium channels remain open for long time and causing the neurons hyper excitable as a result glutamate an excitatory neurotransmitter may be released in large amount form the neurons which by binding with nearby glutamatergic neurons triggers excessive calcium (Ca^{2+}) release in the post synaptic cells 16 which may be neurotoxin to the affected cells [59]. Inflammation has been implicated in the progressive nature of neurodegenerative diseases, and inflammatory processes are now considered key contributors to acute and chronic neurodegenerative disorders, such as ischemic stroke and Alzheimer's disease. In the last decade, experimental and clinical findings support a crucial role of inflammatory processes in epilepsy, in particular in the mechanisms underlying the generation of seizures. Since inflammation represents a homeostatic response to brain injury or pathological threats, its involvement in epilepsy should be envisaged when the extent or duration of inflammatory processes in brain tissue is exceeding the homeostatic threshold.

2-5- Clincical feature of epilepsy

An epileptic seizure is a clinical event; therefore signs and symptoms must feature prominently in the definition. Detailed specification of subjective and objective clinical phenomena during an epileptic seizure is difficult, because Clinical manifestations abnormal enhanced synchrony of the wide range of possible manifestations. Seizure presentation depends on location of onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, sleep–wake cycle, medications, and a variety of other factors. Seizures can affect sensory, motor, and autonomic function; consciousness; emotional state; memory; cognition; or behavior. Not all seizures affect all of these factors, but all

influence at least one. In this context, sensory manifestations are taken to include somatosensory, auditory, visual, olfactory, gustatory, and vestibular senses, and also more complex internal sensations consisting of complex perceptual distortions. In previous definitions, these complex internal sensations were referred to as ―psychic‖ manifestations of seizures.

According to the 2001 ILAE Glossary of Descriptive Terminology for Ictal Semiology [60], cognitive deficits during seizures can appear as problems with perception, attention, emotion, memory, execution, praxis, or speech. Memory distortions can be either negative or positive, in the sense of interruption of memory formation or retrieval as a negative symptom, or intrusion of inappropriate memories as a positive symptom. Positive memory symptoms give rise to other forced memories during seizures. Some of the distorted memories previously were classified as psychic symptoms, which is a potentially ambiguous term. Emotional state is difficult to specify but must be considered in the definition, because some seizures manifest as fear, elation, satisfaction, anxiety, or other subjective sensations that cannot be ascribed to the primary senses [61].

2-6- Diagnosis of epilepsy

Electroencephalography (EEG) has been the most important test in the diagnosis of epilepsy. It involves using a set of electrodes (channels) to record the electrical activity of just those neurons nearest each electrode. When electrical abnormalities are present in some channels of the electroencephalogram and not in others, this pattern localizes the site of the problem. EEG usually is able to detect signs of neuronal dysfunction, even between epileptic attacks (the interracial period), although many epileptic patients have normal interracial EEGs. Evenictal EEGs can be normal if the

seizure is localized to a small area of cortex distant from the recording electrodes. The patient usually undergoes several activation procedures in an attempt to bring out EEG abnormalities. This routinely includes hyperventilation (deep, rapid breathing for 3–5 min) and photic stimulation (flashing lights). However, the most useful activation procedure is sleep or sleep deprivation. The activity of cortical neurons during certain stages of sleep becomes more synchronous than during waking, and this may lead to the appearance of specific abnormal electrical activity strongly suggestive of epilepsy [62].

2-7- Treatment of epilepsy

Epilepsy Drugs to Treat Seizures For 70% of patients with epilepsy, drugs can control seizures. However, they can't cure epilepsy, and most people will need to continue taking medications.

An accurate diagnosis of the type of epilepsy (not just the type of seizure, because most seizure types occur in different types of epilepsy) a person has is very important in choosing the best treatment. The type of medication prescribed will also depend on several factors specific to each patient, such as whom side effects can be tolerated, other illnesses he or she may have, and which delivery method is acceptable.

Below is a list of some of the most common brand-name drugs currently used to treat epilepsy. Your doctor may prefer that you take the brand name of anticonvulsant and not the generic substitution. Talk with your doctor about this important issue.

- **Brivaracetam (Briviact)**

Newly approved in 2016 for use as an add-on treatment to other medications in treating partial onset seizures in patients age 16 years and older.

Possible side effects include drowsiness, dizziness, fatigue, nausea and vomiting.

●Valium can also be given as rectal suppository.

Side effects include tiredness, unsteady walking, nausea, depression, and loss of appetite. In children, they can cause drooling and hyperactivity.

●Eslicarbazepine (Aptiom)

This drug is a once-a-day medication used alone or in combination with other anti- seizure drugs to treat partial-onset seizures.

The most common side effects include dizziness, nausea, headache, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor [(63).]

●Ethosuximide (Zarontin)

Used to treat absence seizures

Adverse effects include nausea, vomiting, decreased appetite, and weight loss.

●Lacosamide (VIMPAT)

This drug is approved to treat partial-onset seizures in adults with epilepsy. VIMPAT can be used alone or with other drugs.

The drug comes as tablets, an oral solution, or injection. Side effects include dizziness, headache, and nausea [64].

●Lamotrigine (Lamictal)

Treats partial, some generalized seizures and mixed seizures.

Has few side effects, but rarely people report dizziness, insomnia, or rash.

●Levetiracetam (Keppra)

It is combined with other epilepsy drugs to treat partial seizures, primary generalized seizures and myoclonic (shock-like jerks of muscle) seizures.

Side effects include tiredness, weakness, and behavioral changes.

●Oxcarbazepine (Oxtellar XR, Trileptal)

Used to treat partial seizures, it is a once-daily medicine used alone or with other medications to control seizures.

Common side effects include dizziness, sleepiness, headache, vomiting, double vision , and balance problems.

●Perampanel (Fycompa)

The drug is approved to treat partial onset seizures and primary generalized tonic- clonic seizures in those aged 12 and older.

The label carries a warning of potential serious events including irritability, aggression, anger, anxiety, paranoia, euphoric mood, agitation, and changes in mental status.

●Phenobarbitol

Oldest epilepsy medicine still in use. It is used to treat most forms of seizures and is known for its effectiveness and low cost.

Side effects can be sleepiness or changes in behavior.

●Phenytoin (Dilantin)

Controls partial seizures and generalized tonic-clonic seizures; also can be given by vein (intravenously) in the hospital to rapidly control active seizures, although if the drug is being delivered by IV, fosphenytoin (Cerebyx) is usually used.

Side effects include dizziness, fatigue, slurred speech, acne, rash, gum thickening, and increased hair (hirsutism). Over the long term, the drug can cause bone thinning.

●Pregabalin (Lyrica)

Used with other epilepsy drugs to treat partial seizures, but is used more often to treat neuropathic pain.

Side effects include dizziness, sleepiness (somnolence), dry mouth, peripheral edema, blurred vision, weight gain, and difficulty with concentration/attention.

●Tiagabine (Gabitril)

Used with other epilepsy drugs to treat partial seizures with or without generalized seizures Common side effects include dizziness, fatigue, weakness, irritability, anxiety, and confusion.

●Topiramate (Topamax)

Used with other drugs to treat partial or generalized tonic-clonic seizures. It is also used with absence seizures.

Side effects include sleepiness, dizziness, speech problems, nervousness, memory problems, visions problems, weight loss [65].

●Valproate, valproic acid (Depakene, Depakote)

Used to treat partial, absence, and generalized tonic-clonic seizures

Common side effects include dizziness, nausea, vomiting, tremor, hair loss, weight gain, depression in adults, irritability in children, reduced attention, a decrease in thinking speed. Over the long term, the drug can cause bone thinning, swelling of the ankles, irregular menstrual periods. More rare and dangerous effects include hearing loss, liver damage, decreased platelets (clotting cells), and pancreas problems.

●Zonisamide (Zonegran)

Used with other drugs to treat partial, generalized and myoclonic seizures

Adverse effects include drowsiness, dizziness, unsteady gait, kidney stones, abdominal discomfort, headache, and rash [66].

Chapter 3

Material and method

3.1 Study type and design

Descriptive Cross Sectional Study

3-1-2Study population

Sudanese patients professionally diagnosed with psychological disorders.

3-1-3Study area

Eltigani Elmahi Neurological and Psychological Hospital-Khartoum state-Sudan.

3-1-4Inclusion criteria

Patients involved in this study were diagnosed with abnormal Neurological and psychological disorders and had seizures and under valporic acid treatment

3-1-5Exclusion criteria

Patients with other disorders rather than epilepsy related psychological disorders did not involve in this study, such as leukemia, T2DM and others.

3-1-6Sample size

A total number of 199 persons were included in the study. The cases were 99 patients and 100 persons were control.

3-1-7Ethical consideration

This study was approved by the ethical committee of Shandi University-Faculty of Graduate, the hospital administration and patient‘s legal guardians to be parts of this study.

3-1-8 Data collection

Data collection was performed with direct well-constructed questionnaire included age, gender and duration of drug administration.

3-2 Analytical phase

3-2-1Material required

Table (3.1) 1Material required

Items	**Need**	**Quantity**
70% alcohol	Disinfection	1 liter
Cotton and bandages	Swap to disinfect area of needle	2 folds
Syringes	Blood withdraw	200
EDTA containers	Blood collection	200
Sysmex kx 21	CBC performance	1
Diluent reagent	RBC lysing agent for sysmex Kx 21.	20 liters
Stomatolyser reagent	Dilution of blood samples for sysmex kx 21	500 ml

3-2-3Sample collection

Under hygienic conditions, using 70% alcohol and pre-analytical phase preparation of patients and equipment, 3 ml of blood collected in ethylene diamine tetra acetic acid (EDTA) added blood container from each patients, transferred to the lab zone for measurement of hematological parameters.

3-2-4 Method of analysis

For in vitro diagnostic use in clinical laboratories manufactured by TOA medical electronics company this instrument is capable of performing speedy (processes approximately 60 samples per hour) and accurate analysis of 19 parameters in blood and detect the abnormal samples on LCD screen.

The KX_21N employs three detector blocks and two kinds of reagents for blood analysis.

- The WBCs detector block using DC detection method measures the WBCs count.
- The RBCs count and platelets are taken by the RBCs detector block also using the DC detection method.
- The HGB detector block measures the hemoglobin concentration using the non- cyanide hemoglobin method

Principle:

I/Cell detection in hematology instrumentation based on three principles: I/ Increased electrical impedance.

II/ Deflection of radio wave.

III/ Optical scattering of laser beam.

IV/ DC (electrical impedance) detection methods

Blood always aspirated in measured volume. Diluted at specific ratio and then fed in to each transducer the transducer chamber has a minute hole called the aperture on both site of the aperture there are the electrodes between which flows direct current.

Blood cell suspension (electrolyte solution in the diluted sample pass through the aperture. Causing direct current resistance to change between the electrodes as direct current resistance changes the blood cell size is detected as electric plus .a high voltage is needed to maintain constant current in the case of increased electrical resistance an electric plus proportional to the voltage is generated by the instrument blood cell count is calculated by counting the pulses (i.e., The number of pulses yields the particles count)¸ the amplitude of each electrical pulse correlates with the cell size and a histogram (a bar chart with equal width to each bar) of blood cell size is plotted by determining the pulse size range. Also analyzing a histogram makes it possible to obtain various analysis data.

After inserting blood sample to be measured, the result would be displayed after approximately 40 seconds on laser crystal display (LCD), and then the instrument cleans all tubes to be ready for next sample by displaying (Ready) status.

3.3 Data analysis

Data obtained was statistically analyzed with statistical package of social science (program) version 21.

Chapter 4

Result

4-Result

This descriptive cross- sectional study involved patients with epileptic episodes attended to Eltigani Elmahi Neurological and psychological Hospital - Khartoum state Omdurman region, They were under valporic acid treatment as it antiepileptic drug. They were 53(58%) males and 38 (42%) females as in figure 4-1.

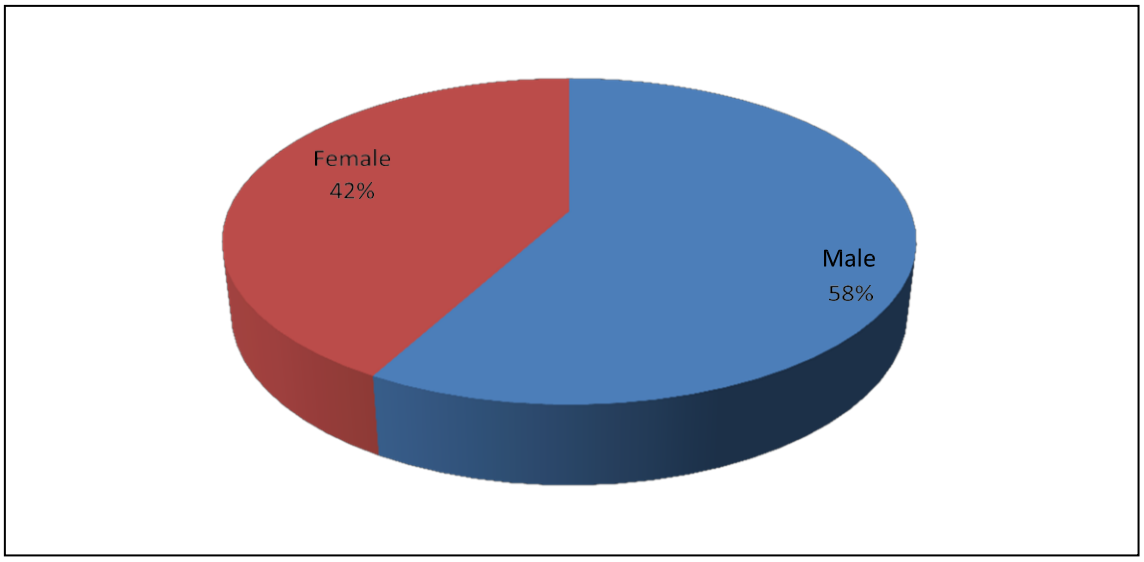

Figure 4-1: distribution of patients according to gender

Independent T-test between patients (case group) and healthy individuals (control group), showed that for RBCs parameters; RBC, Hb and PCV were increased among case group than control group giving significant difference, while other RBC related indices MCH and MCHC were decreased among case group than control group giving significant difference. WBC related parameters: TWBC, N% and L% were decreased among case group than control group giving significant difference. And platelet related parameters: platelet count was decreased among case group than control group, while

platelet indices PDW, MPV and P-LCR were increased among case group, and all platelet parameters gave significant difference as in table (4-1)

Table (4-1) Mean comparison of study group in case versus control group

Parameters	Case (Mean±SD)	Control (Mean±SD)	*P-value*
RBC	4.78±0.49	4.44±0.60	0.000
Hb	13.29±1.78	12.68±2.14	0.034
PCV	42.38±5.45	38.28±6.92	0.000
MCV	86.95±7.82	84.56±10.82	0.085
MCH	27.56±1.79	28.55±2.43	0.002
MCHC	31.06±2.16	32.50±3.77	0.002
RDW-CV	13.55±0.94	13.58±2.11	0.899
TWBC	6.27±1.88	7.22±4.16	0.047
N %	53.48±13.95	57.51±12.99	0.041
L %	36.57±11.20	30.94±11.58	0.001
M %	6.36±4.23	12.81±4.34	0.079
Plate	208.09±100.99	275.12±101.70	0.000
PDW FL	13.58±2.01	11.96±2.68	0.000
MPV FL	10.46±0.95	9.68±1.46	0.000
P-LCR	29.23±7.03	24.57±14.13	0.005

Significant difference P. value <0.05

Considering gender distribution, only RBC related parameters, RBCs, Hb, and PCV were increased among males than females, with significant difference 0.004,

0.03 and 0.002 respectively, while other complete blood count parameters did not give significant difference as in table (4-2)

Table (4-2) Mean comparison of study group across the gender

Parameters	Male (Mean±SD)	Female (Mean±SD)	*P-value*
RBC	4.91±0.46	4.60±0.49	0.004
Hb	13.63±2.00	12.81±1.29	0.030
PCV	43.89±6.12	40.29±3.46	0.002
MCV	86.64±9.53	87.37±4.53	0.664
MCH	27.77±1.72	27.26±1.87	0.181
MCHC	31.07±2.62	31.05±1.29	0.974
RDW-CV	13.51±0.85	13.60±1.05	0.643
TWBC	6.01±1.61	6.64±2.16	0.113
N %	53.74±14.21	53.11±13.75	0.835
L %	35.91±11.95	37.51±10.12	0.506
M %	6.17±4.27	6.62±4.22	0.621
Plate	203.24±102.36	214.84±100.02	0.592
PDW FL	13.73±2.06	13.36±1.95	0.396
MPV FL	10.49±0.99	10.42±0.91	0.730
P-LCR	29.43±7.28	28.94±6.74	0.742

Significant difference P. value <0.05

Considering dosage of valporic acid, the patients were sorted to group of less than 1 gram and group more than 1 gram, the only affected parameter was the MCH, as it was increased among case group than control group with significant difference as p vale 0.041, as in table(4-3)

Table (4-3) mean comparison of study group across dose/g

Parameters	<1/g (Mean±SD) g/day	≥1/g (Mean±SD) g/day	*P-value*
RBC	4.66±0.41	4.81±0.51	0.251
Hb	13.55±0.92	13.22±1.93	0.487
PCV	41.94±3.26	42.49±5.88	0.705
MCV	88.67±4.91	86.52±8.35	0.299
MCH	28.28±1.64	27.38±1.79	0.041
MCHC	31.33±0.77	30.99±2.38	0.554
RDW-CV	13.67±0.75	13.52±0.98	0.535
TWBC	6.93±2.04	6.11±1.81	0.095
N %	51.24±13.11	54.00±14.18	0.465
L %	37.59±14.96	36.33±10.25	0.679
M %	7.76±5.34	6.03±3.90	0.128
Plate	162.22±112.15	219.40±95.52	0.031
PDW FL	13.71±2.15	13.54±1.99	0.752
MPV FL	10.63±0.88	10.42±0.97	0.422
P-LCR	30.99±6.18	28.79±7.19	0.235

Significant difference P. value <0.05

Pearson correlation with study parameters and age, gave positive correlation with RBC, MCV, MCHC, RDW-CV, TWBC, L%, and platelet count, while the rest of parameters have negative correlation as in table(4-4)

Table (4-4) correlation between study parameters and age

Parameters	*R-value*	*P-value*
RBC	0.002	0.985
Hb	-0.015	0.887
PCV	-0.092	0.386
MCV	0.080	0.453
MCH	-0.049	0.645
MCHC	0.115	0.277
RDW-CV	0.171	0.105
TWBC	0.017	0.870
N %	-0.192	0.070
L %	0.088	0.409
M %	-0.057	0.595
Plate	0.005	0.964
PDW FL	-0.041	0.703
MPV FL	-0.138	0.191
P-LCR	-0.149	0.157

Pearson correlation with study parameters and dose duration, gave positive correlation with RBC, Hb, MCV, MCHC, RDW-CV, TWBC, L%, M %, and platelet indices MPC and P-LCR, while the rest of parameters have negative correlation as in Table (4.5)

Table (4-5) correlation between study parameters and dose duration

Parameters	*R-value*	*P-value*
RBC	0.023	0.828
Hb	0.014	0.896
PCV	-0.049	0.642
MCV	0.048	0.648
MCH	-0.121	0.253
MCHC	0.025	0.813
RDW-CV	-0.019	0.855
TWBC	0.015	0.884
N %	-0.137	0.197
L %	0.161	0.107
M %	0.107	0.314
Plate	-0.094	0.374
PDW FL	-0.134	0.206
MPV FL	0.012	0.913
P-LCR	0.014	0.894

Chapter 5

Discussion

5-Discussion

This study, complete blood count for patients under anti-epileptic drug, mainly valporic acid were under consider, to evaluate the effects of antiepileptic drug (Valporic Acid) which is s drug of choice, on complete blood count in epileptic patients under treatment duration and its dose of the measure parameters, which were compared with parameters of control group of healthy individuals with no symptoms of illness mentally or physically. Complete blood count parameters measure were red blood cell parameters, RBC, Hb, PCV, MCV, MCH, MCHC and RDW-CV, it showed that there were differences in the mean of the parameter‘s gave significant, such as RBC, Hb and PCV were increased among patients than control individuals, other difference obtained with MCH and MCHC, they both were decreased among patients than control, and the rest of red cell parameters did not affected among case group, no anemia was found among patients, *this in disagreement of study depended on the fact that valporic acid may cause hematological abnormality, as in a case study on a patient with seizure and prescribed for valporic acid, for the 12months of treatment, the patient was suffering from anemia, and the period after stopped, anemia has been corrected and vanished with the time after that [(67).]

In this study, white blood cell‘s parameters, contained TWBC, N for neutrophil%, L for lymphocyte % and M for monocyte %, all were decreased among patients except the L%, than control group, also platelet parameters included platelet count, MPV, PDW and P-LCR. Platelet count was decreased among case group, while the rest of the parameters were increased among the patients. Not many studies among psychotic patients were conducted included white blood cell and platelet, most of them carried

on due to symptoms of bleeding which mostly related to thrombocytopenia, and the patient was under other drug than valporic acid.

Other studies in agreement with this study on the side of platelet affected by valporic acid it mentioned that, all anti-epileptic drugs considered potential toxic drugs; as all have significantly impaired hematological profile of the epileptics. Platelet count was significantly reduced in epileptics treated with several kinds of anti-epileptic drugs included VPA as monotherapy or combination therapy compared to newer AEDs combination therapy.[68, 69 & 70]

Chapter 6

Conclusion and recommendation

6-1Conclusion

Valporic acid has effect on platelet more than other parameters of the complete blood count, regardless the age, duration or the dose of the drug, white blood cell were low, but within range of normal but hemoglobin and related red blood cell parameters were high among case group.

6-2 Recommendation

Regular laboratory assessment should be performed including CBC and other parameters to avoid side effects if they occurred to save lives.

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Appendices (1):

بسم الله الرحمن الرحيم

جامعـــــة شنـــــدي

كلية الدراسات العليا والبحث العلمي

مركز الخرطوم

النمرة : ج ش/ك د ع /م خ ا 25/2/2018

إلى من يهمهم الأمر بإدارة التدريب – مستشفى التجاني الماحي

المحترمين

السلام عليكم ورحمة الله وبركاته

الموضوع : الطالبة/نجلاء عبدالحفيظ محمد جميل

بالإشارة إلى الموضوع أعلاه نفيدكم بأن الطالبة المذكورة أعلاه من ضمن طلاب الكلية بالفصل الدراسي الرابع – ببرنامج ماجستير علوم المختبرات الطبية ، تخصص أمراض الدم، وهي بغرض توزيع استبانة لدراسة الحالة وجمع العينات للبحث التكميلي والذي عنوانه :

Effects of antiepliephic drugs (valporicacid) on complete blood count perrameters among Sudanese with Eepileptic Episodes.

نرجو تيسير مهمتها البحثية .

ولكم فائق الشكر والتقدير،،،،

الصادق أحمد عبدالقادر

مسجل المركز

Appendices (2):

Questionnaire

Age……..

Gender…….

Duration of drug administration……

Dose……..

Appendices (3):

Device used

K X 21