IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 16, Issue 2 Ser. II (Mar. – Apr. 2021), PP 14-19
www.Iosrjournals.Org

Antiepileptic-Induced Nutritional Deficiencies

Sowmya. Besu[1], Jyothsna. Nedhnuri[2], Pawan kalyan. Dandiyala[3]

Date of Submission: 20-03-2021 Date of Acceptance: 04-04-2021

I. Introduction:

Epilepsy

A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. "Epileptic seizure" is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. "Epilepsy" is the condition of recurrent, unprovoked seizures.

Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per 100,000 population every year [1]. About 1% of the total population suffers from epilepsy from which one-third are refractory epilepsy patients Approximately 75% of epilepsy begins during childhood, reflecting the susceptibility of the developing brain to seizures.

A seizure can be defined as occurring when there is disturbance of the normal balance between excitation (E) and inhibition (I) in the brain [2] This E/I imbalance can result from an alteration at many levels of brain function, from genes and subcellular signalling cascades to widespread neuronal circuits. The factors that alter E/I balance can be genetic or acquired. Genetic pathologies leading to epilepsy can occur anywhere from the circuit level to the receptor level to abnormal ionic channel function. Similarly, acquired cerebral insults can alter circuit function. The developing brain is particularly prone to seizures for a variety of physiological reasons [3]. Even in the normal developing brain, excitatory synaptic function develops before inhibitory synaptic function, favouring enhanced excitation and seizure generation. In addition, early in life, the neurotransmitter GABA causes excitation rather than inhibition [4]. These observations partly explain why the very young brain is especially susceptible to seizures. However, seizures cause less structural damage in the developing brain than in the adult brain [5]. Recent explosions showed both monogenic and polygenic mutations can lead to epilepsy [6]. Many epilepsies have a complex genetic basis with multiple gene defects contributing to a state of altered cellular excitability, which underlies epilepsy. As genetics knowledge expands, there is hope that syndrome-specific therapeutic interventions can be designed [7].

Epilepsy is more than spontaneous recurrent seizures and should be considered a disorder. For many patients and families, the burden of the disease is largely caused by comorbid conditions, including behavioural and psychiatric disorders, such as depression, anxiety, learning disabilities, attention-deficit hyperactivity disorder, intellectual disability, and autism. These comorbidities, previously considered to be secondary to uncontrolled seizures or medication adverse effects, are now recognized as an integral part of the disorder, sometimes even preceding the seizures and attributable to an underlying disorder of neuronal networks [8]. Even a single seizure can alter neurodevelopment by modifying receptor expression and distribution in the absence of neuronal death, leading to cognitive and behavioural changes [9]. A survey by National Health Interview showed, adults with epilepsy had a higher prevalence of cardiovascular and respiratory disorders, diabetes, inflammation, obesity, and other disorders [10] (e.g., headache, migraine, arthritis). Persons with epilepsy are also at increased risk for early mortality and sudden unexplained death in epilepsy [11] (SUDEP). Recently, the impact of seizure medication on bone health has become a major concern. Patients with epilepsy are at high risk for fractures because of lower bone mineral density (BMD) [12].

Antiepileptic medications

Phenytoin, phenobarbital, and carbamazepine appear to be the antiseizure medications that lead to a reduction in BMD via induction of the CYP450 enzyme system results, but osteopenia has also been reported with non-enzyme-inducing AEDs. Most AEDs undergo complete or nearly complete absorption when given orally. Most often, administration of AEDs with food slows absorption and can help avert peak dose related side effects. Lipid solubility and protein binding affect CNS availability. Drug interactions between albumin and protein binding leads to AEDs side effects [13].

Most AEDs are metabolized in the liver by P450 enzyme system by hydroxylation or conjugation. These metabolites are then excreted by the kidney. Some metabolites are themselves active (carbamazepine, oxcarbazepine, primidone). Gabapentin undergoes no metabolism and is excreted unchanged by the kidney.

Valproic acid is metabolized by a combination of conjugation by uridine glucuronate (UDP)-Glucuronyltranferase (UGT) via conjugation and by mitochondrial beta-oxidation. Enzyme-inducing antiepileptic drugs (AEDs) produce a considerable number of metabolic alterations, including changes in serum lipids, hormones, bone turnover, and various vitamin levels.

Chemical Class	Examples of antiepileptic drug
Barbiturates	Phenobarbitone, Mephobarbitone, Primidone
Hydantoins	Phonations, Mephenytoin
Iminostilbene	Carbamazepine
Oxazolidinedione	Trimethadione (Troxidone)
Succinimide	Ethosuximide
Aliphatic Carboxylic acid	Valproic acid (Sodium valproate)
Benzodiazepines	Clonazepam, Diazepam
Acetyl urea	Phenacemide
Newer drugs	Progabide, Vigabatrin, Gabapentin Lamotrigine, Felbamate, Topiramate, Tiagabine
Miscellaneous	Acetazolamide, Dexamphetamine

fig.1 antiepileptic drug classification with examples.

Mechanism of action

A seizure is the clinical manifestation of a hyperexcitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered—excitation predominates over inhibition. Effective seizure treatment generally augments inhibitory processes or opposes excitatory processes. Since the normal resting neuronal membrane potential is intracellularly negative, inhibitory processes make the neuron more electrically negative, hyperpolarizing the membrane, while excitatory processes make the intracellular potential less negative or more positive, depolarizing the cell. On an ionic level, inhibition is typically mediated by inward chloride or outward potassium currents, and excitation by inward sodium or calcium currents. Drugs can directly affect specific ion channels or indirectly influence synthesis, metabolism, or function of neurotransmitters or receptors that control channel opening and closing. The most important central nervous system inhibitory neurotransmitter is gamma-amino-butyric acid (GABA). The most important excitatory neurotransmitter is glutamate, acting through several receptor subtypes. The major mechanism of action of AEDs is by blocking voltage-gated sodium channels during rapid rates of neuronal discharge appears to be the primary mechanism of action of several AEDs, particularly the two first-line drugs for partial epilepsies, phenytoin and carbamazepine; this mechanism also appears to be at least partly responsible for the antiepileptic effects of newer drugs such as lamotrigine and topiramate [14-16].

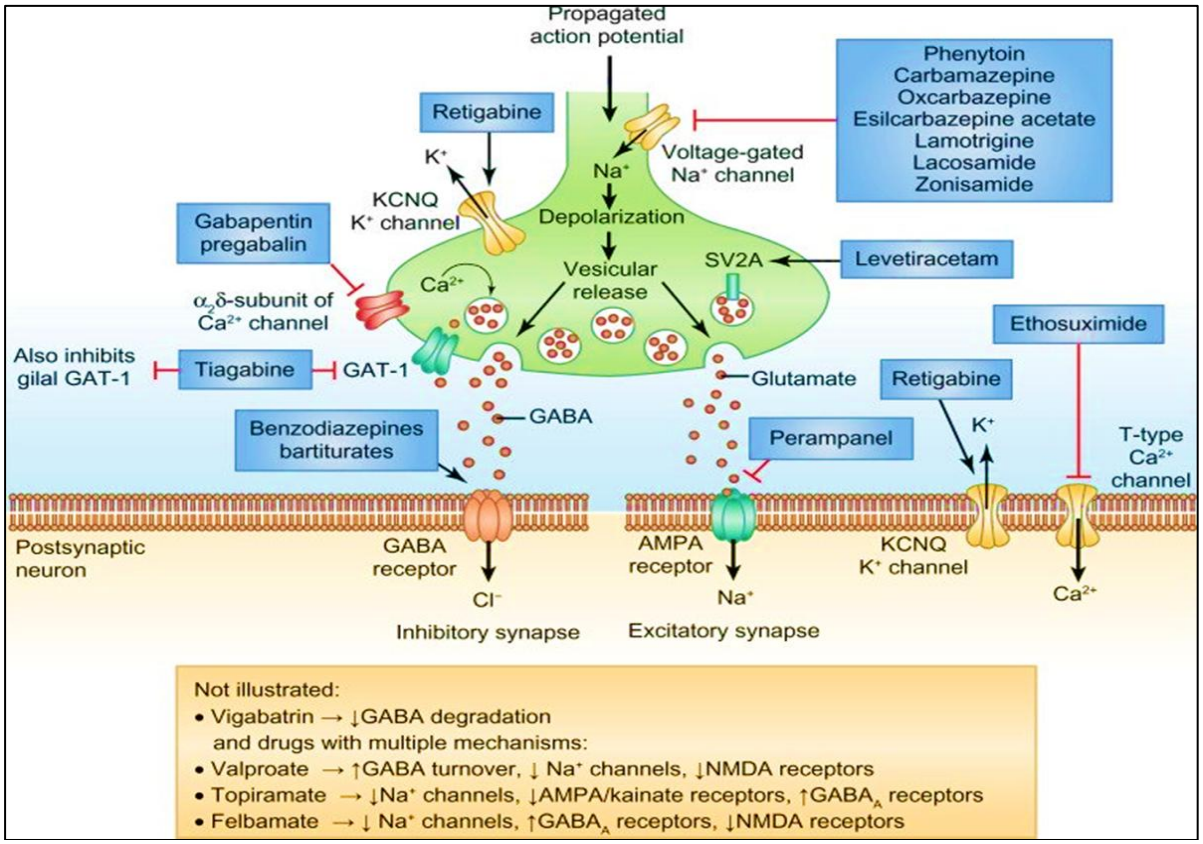

fig.2 mechanism of action of antiepileptic drugs.

Adverse drug reactions:

AEDs have a narrow therapeutic window—a small range of serum concentrations within which seizure prevention is achievable without significant toxicity or side effects. This concept applies primarily to dose-related, reversible, short-term side effects. However, risk of idiosyncratic effects such as allergic reactions and organ damage must also be considered. Serious idiosyncratic effects are rare but can be life threatening. They generally occur within several weeks or months of starting the drug, tend to be dose-independent (except possibly for skin rash with lamotrigine), and unpredictable.

NUTRITIONAL DEFICIENCIES:

Vitamin-D

Vitamin D levels are influenced by several other important factors including dietary vitamin D and calcium intake, physical activity, and medications that may affect vitamin D levels [17] Antiepileptic drug (AED) therapy for long term use may also lead to vitamin D deficiency and impaired bone health in epileptic children. There are now recommendations to periodically monitor blood levels and supplementation of vitamin D in children on long-term use of AEDs [18-20] Seizures, neuromotor dysfunction, immobilization, polytherapy and long-term drug treatment negatively influence bone health, which can be aggravated by vitamin D deficiency [21]. Many studies have postulated vitamin D deficiency in epileptic children which showed 25-hydroxyvitamin D [25(OH)D] is main cause of hypovitaminosis D in AED therapy.

Vitamin-B

Vit-B6 deficiency may also lead to anemia and may increase the risk of a number of cancers [27]. AEDs induced vitamin B6 deficiency mechanism is unclear. B6 is oxidized in the liver prior to urinary excretion [27], and such oxidizing enzymes are frequent targets of enzyme inducers, so that it is likely that increased activity of the oxidizing enzyme in the presence of PHT or CBZ results in increased catabolism of B6. Example isoniazid an antitubercular drug which forms a complex with B6 and thus reduces the availability of it to tissues and it is standard therapy that vitamin supplements are prescribed along with isoniazid [22]. This neuropathic action of isoniazid and the present findings are of interest in light of the evidence that PHT may be neuropathic [23,24]. There is also evidence that other inducing AEDs may contribute to the development of peripheral neuropathy [25,26] It is not clear that B6 deficiency contributes to seizures in adults or older children lacking the relevant

mutation, though a recent case series suggested B6 deficiency as a cause of new-onset refractory seizures in several critically ill patients [27].

Folic acid

Folic acid deficiency is associated with megaloblastic anemia but in some it causes neurological deficiency when associated with vitamin deficiency. In women with epilepsy low red blood cells folate, causes malformations and termination of pregnancy. Folic acid deficiency is associated with increase in levels of homocysteine which is predominantly increased by AED therapy. A study on AED therapy showed CBZ and PHT, phenobarbital and primidone leads to folic acid deficiency in some patients. Hyperhomocysteinemia is associated with vascular disease, cerebrovascular disease, and in some neurodegenerative disorders. A study showed neural tube defects are more frequent in infants born to mothers with low folic acid deficiency. Hyperhomocysteinemia is treated with vitamin B12, vitamin D6, and folic acid suppliments [28-31].

Calcium

Biochemical abnormalities in adults receiving AEDs include hypocalcemia, hypophosphatemia, reduced levels of active vitamin D metabolites, elevated parathyroid hormone (PTH) levels, and elevated markers of bone resorption and formation. the Vit-d deficiency in patients treated with AED therapy leads to decrease in calcium and increase in parathyroid hormone which leads to further bone resorption and bone disease [32,33]. In contrast, one study of patients taking valproate found hypercalcemia. The elevated serum calcium was postulated to reflect increased bone resorption.

Mechanisms of AED-Associated Bone Disease

Several theories have been proposed to explain the link between AEDs and bone disease. There are multiple mechanisms for AEDs induced bone deficiency. Increased catabolism of vitamin D, resulting from hepatic induction of the cytochrome P450 enzyme system, is the principal mechanism reported. However, it does not explain the findings described in patients receiving other medications, such as valproate (an inhibitor of the cytochrome P450 enzyme system), or the recent evidence of increased bone turnover independent of vitamin D deficiency. Levels of active vitamin D metabolites may be reduced in persons taking enzyme-inducing AEDs, suggesting that induction of hepatic cytochrome P450 enzymes partially explain the findings in bone. [34-36] The AEDs that induce cytochrome P450 enzymes may cause increased conversion of vitamin D to polar inactive metabolites in the liver microsomes, reducing levels of bioavailable vitamin D. [36,37] Reduced levels of biologically active vitamin D lead to decreased absorption of calcium in the gut, resulting in hypocalcemia and an increase in circulating PTH. PTH then increases the mobilization of bone calcium stores and subsequent bone turnover. Impairment of calcium absorption is another postulated mechanism, as AEDs may interfere with intestinal absorption of calcium. Impaired absorption would lead to hypocalcemia and feedback hypersecretion of PTH. Phenytoin plays a key role in bone resorption in patients treated with AED therapy. The other deficiencies caused by AED therapy is shown in fig3.

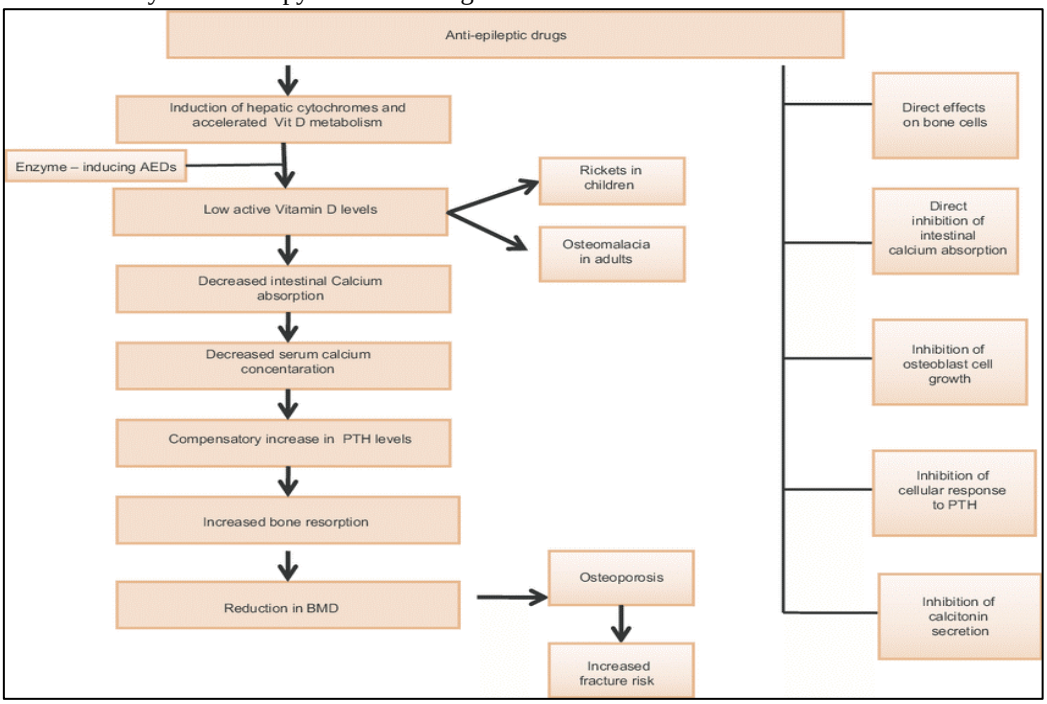

fig.3 Antiepileptic drugs induced nutritional deficiencies.

Treatment of AED induced bone disease

Treatment for AED induced bone disorders include vitamin D supplementation, bisphosphonates, calcium supplements and hormone replacement therapy, selective estrogen receptor modulators and calcitonin. Vitamin K supplementation

1. High dose vitamin D supplementation
2. Calcium supplementation.
3. Bisphosphonates
4. Hormone replacement therapy
5. Selective estrogen receptor modulators
6. Calcitonin
7. Vitamin K supplementation

References

[1]. Hauser, W. A. (1990). Epilepsy: frequency, causes and consequences. *Epilepsy Found Am*, *275*.

[2]. Rho, J., Sankar, R., & Stafstrom, C. E. (Eds.). (2010). *Epilepsy: mechanisms, models, and translational perspectives*. CRC Press.Berkovic SF. 2015. Genetics of epilepsy in humans. Cold Spring Harb Perspect Med doi: 10.1101/cshperspect .a022400.

[3]. Ben-Ari, Y. (2002). Excitatory actions of gaba during development: the nature of the nurture. *Nature Reviews Neuroscience*, *3*(9), 728-739.

[4]. Holmes, G. L., & Ben-Ari, Y. (1998). Seizures in the developing brain: perhaps not so benign after all. *Neuron*, *21*(6), 1231-1234.

[5]. Poduri, A., & Lowenstein, D. (2011). Epilepsy genetics—past, present, and future. *Current opinion in genetics & development*, *21*(3), 325-332.

[6]. Thomas, R. H., & Berkovic, S. F. (2014). The hidden genetics of epilepsy—a clinically important new paradigm. *Nature Reviews Neurology*, *10*(5), 283.

[7]. Brooks- Kayal, A. R., Bath, K. G., Berg, A. T., Galanopoulou, A. S., Holmes, G. L., Jensen, F. E., ... & Scharfman, H. E. (2013). Issues related to symptomatic and disease- modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia*, *54*, 44-60.

[8]. Cornejo, B. J., Mesches, M. H., Coultrap, S., Browning, M. D., & Benke, T. A. (2007). A single episode of neonatal seizures permanently alters glutamatergic synapses. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *61*(5), 411-426.

[9]. Strine, T. W., Kobau, R., Chapman, D. P., Thurman, D. J., Price, P., & Balluz, L. S. (2005). Psychological distress, comorbidities, and health behaviors among US adults with seizures: results from the 2002 National Health Interview Survey. *Epilepsia*, *46*(7), 1133-1139.

[10]. Surges, R., & Sander, J. W. (2012). Sudden unexpected death in epilepsy: mechanisms, prevalence, and prevention. *Current opinion in neurology*, *25*(2), 201-207.

[11]. Beerhorst, K., van der Kruijs, S. J., Verschuure, P., Tan, I. F., & Aldenkamp, A. P. (2013). Bone disease during chronic antiepileptic drug therapy: general versus specific risk factors. *Journal of the neurological sciences*, *331*(1-2), 19-25.

[12]. Hanaya, R., & Arita, K. (2016). The new antiepileptic drugs: their neuropharmacology and clinical indications. *Neurologia medico-chirurgica*, ra-2015.

[13]. Czapinski, P., Blaszczyk, B., & Czuczwar, S. J. (2005). Mechanisms of action of antiepileptic drugs. *Current topics in medicinal chemistry*, *5*(1), 3-14.

[14]. White, H. S., Smith, M. D., & Wilcox, K. S. (2007). Mechanisms of action of antiepileptic drugs. *International review of neurobiology*, *81*, 85-110.

[15]. Davies, J. A. (1995). Mechanisms of action of antiepileptic drugs. *Seizure*, *4*(4), 267-271.

[16]. Saggese, G., Vierucci, F., Boot, A. M., Czech-Kowalska, J., Weber, G., Camargo, C. A., ... & Holick, M. F. (2015). Vitamin D in childhood and adolescence: an expert position statement. *European journal of pediatrics*, *174*(5), 565-576.

[17]. Shellhaas, R. A., & Joshi, S. M. (2010). Vitamin D and bone health among children with epilepsy. *Pediatric neurology*, *42*(6), 385-393.

[18]. Yildiz, E. P., Poyrazoglu, Ş., Bektas, G., Kardelen, A. D., & Aydinli, N. (2017). Potential risk factors for vitamin D levels in medium-and long-term use of antiepileptic drugs in childhood. *Acta Neurologica Belgica*, *117*(2), 447-453.

[19]. Cebeci, A. N., & Ekici, B. (2014). Epilepsy treatment by sacrificing vitamin D. *Expert review of neurotherapeutics*, *14*(5), 481-491.

[20]. Harijan, P., Khan, A., & Hussain, N. (2013). Vitamin D deficiency in children with epilepsy: Do we need to detect and treat it?. *Journal of pediatric neurosciences*, *8*(1), 5.

[21]. Kosyfaki, P., Woerner, W., & Att, W. (2011). Prosthodontic treatment in a partially edentulous patient with a complex medical history of epilepsy and deep vein thrombosis: A case report. *Quintessence International*, *42*(5).

[22]. Grover, P. J., Jayaram, R., & Madder, H. (2010). Management of cerebral venous thrombosis in a patient with Lane-Hamilton syndrome and coeliac disease, epilepsy and cerebral calcification syndrome. *British journal of neurosurgery*, *24*(6), 684-685.

[23]. Brazzelli, V., Grasso, V., Fornara, L., Moggio, E., Gamba, G., Villani, S., & Borroni, G. (2010). Homocysteine, vitamin B12 and folic acid levels in psoriatic patients and correlation with disease severity. *International journal of immunopathology and pharmacology*, *23*(3), 911-916.

[24]. Salemi, G., Gueli, M. C., D'Amelio, M., Saia, V., Mangiapane, P., Aridon, P., ... & Lupo, I. (2009). Blood levels of homocysteine, cysteine, glutathione, folic acid, and vitamin B 12 in the acute phase of atherothrombotic stroke. *Neurological sciences*, *30*(4), 361-364.

[25]. Cakmak, S. K., Gül, Ü., Kılıç, C., Gönül, M., Soylu, S., & Kılıç, A. (2009). Homocysteine, vitamin B12 and folic acid levels in psoriasis patients. *Journal of the European Academy of Dermatology and Venereology*, *23*(3), 300-303.

[26]. Zhou, K., Zhao, R., Geng, Z., Jiang, L., Cao, Y., Xu, D., ... & Zhou, J. (2012). Association between B-group vitamins and venous thrombosis: systematic review and meta-analysis of epidemiological studies. *Journal of thrombosis and thrombolysis*, *34*(4), 459-467.

[27]. Kaneko, S., Otani, K., Fukushima, Y., Ogawa, Y., Nomura, Y., Ono, T., ... & Goto, M. (1988). Teratogenicity of antiepileptic drugs: analysis of possible risk factors. *Epilepsia*, *29*(4), 459-467.

[28]. Dansky, L. V., Andermann, E., Rosenblatt, D., Sherwin, A. L., & Andermann, F. (1987). Anticonvulsants, folate levels, and pregnancy outcome: a prospective study. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *21*(2), 176-182.
[29]. Hiilesmaa, V. K., Teramo, K., Granström, M. L., & Bardy, A. H. (1983). Serum folate concentrations during pregnancy in women with epilepsy: relation to antiepileptic drug concentrations, number of seizures, and fetal outcome. *Br Med J (Clin Res Ed)*, *287*(6392), 577-579.
[30]. Diaz-Arrastia, R. (2000). Homocysteine and neurologic disease. *Archives of neurology*, *57*(10), 1422-1427.
[31]. Perucca, E. (1987). Clinical implications of hepatic microsomal enzyme induction by antiepileptic drugs. *Pharmacology & therapeutics*, *33*(1), 139-144.
[32]. Koch, H. U., Kraft, D., Herrath, D. V., & Schaefer, K. (1972). Influence of diphenylhydantoin and phenobarbital on intestinal calcium transport in the rat. *Epilepsia*, *13*(6), 829-834.
[33]. Hahn, T. J., Hendin, B. A., Scharp, C. R., & Haddad Jr, J. G. (1972). Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. *New England Journal of Medicine*, *287*(18), 900-904.
[34]. Hoikka, V., Savolainen, K., Alhava, E. M., Sivenius, J., Karjalainen, P., & Repo, A. (1981). Osteomalacia in institutionalized epileptic patients on long- term anticonvulsant therapy. *Acta Neurologica Scandinavica*, *64*(2), 122-131.
[35]. Gough, H., Goggin, T., Bissessar, A., Baker, M., Crowley, M., & Callaghan, N. (1986). A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. *QJM: An International Journal of Medicine*, *59*(3), 569-577.
[36]. Perucca, E. (1987). Clinical implications of hepatic microsomal enzyme induction by antiepileptic drugs. *Pharmacology & therapeutics*, *33*(1), 139-144.

Sowmya. Besu, et. al. "Antiepileptic-Induced Nutritional Deficiencies." *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 16(2), (2021): pp. 14-19.