Role of Vitamin D in Childhood Epilepsy

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Abstract

Background: Vitamin D is a fat-soluble vitamin and also considered a steroid hormone, that plays an important role in the proper functioning of many organs of the body.Adequate vitamin D status plays a very important role in terms of appropriate brain development and function .Regarding vitamin D, it's participation in the central nervous system's function is corroborated by the presence of the enzyme 25(OH)D3-1alpha-hydroxylase, which form of the active form of vitaminD, and the presence of receptors of vitamin D (VDR) in the brain tissue , mostly in the hypothalamus and substantia nigra. The aim of this review: is to evaluate the roleof vitamin D in childhood epilepsy and to study the vitamin D –antiepleptic drugs interactions among epileptic children.

Conclusion: vitamin D insufficiency and deficiency are highly prevalent among children with epilepsy.A lot of antiepileptic drugs lower vitamin D level and lead to more seizures specially enzyme inducers' drugs.

Keywords: Vitamin D, Epilepsy, Antiepileptic drugs.

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Introduction

Vitamin D includes a lot of secosteroids which relate structurally and is sub-classified, humans into vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), which slightly show more efficacy **(Tripkovic et al .,2012).** Both playa very important role in calcium and phosphorus homeostasis **(Holick, 2007)**.Vitamin D3 is the primary source for humans, in the skin from provitamin D3 (7-dehydrocholesterol) upon ultraviolet B exposure, animal-derived foods rich in oily fish is the main, non-fortified dietary sources of provitamin D3 **(Lehmann et al.,2015)**.Some plant sources also contain small concentrations of vitamin D2**(Japelt ,Jakobsen 2013)** as, e.g., sun-exposed). mushrooms **(Lu et al .,2007).**

1.1- Vitamin D metabolism

Formation of either 1,25-dihydroxyvitamin D3 (calcitriol, 1,25(OH)2D3) or 1,25- dihydroxyvitamin D2(ergocalcitriol, 1,25(OH)2D2),involves two chemical processes of hyroxylation,**(Vieth 2004).**Both are multiple secosteroid hormones that adjust the expression of more than 900 genes **(Pike et al .,2010)**this process occurs by formation of a bond with vitamin D receptor (VDR) a receptor of a steroid hormone, which after formation of a VDR/retinoid-X receptor/cofactor complex works as a nuclear transcription agent**(Ryan et al .,2015)**, thus deficiency of vitamin D can also considered a hormonal deficiency **(Christakos et al .,2016).**

1.2-Vitamin D Homeostasis

Vitamin D sources include dairy nutrient intakes and fish oils of diet, it also formed in the skin by ultraviolet irradiation from 7-dehydrocholesterol .Vitamin D-binding protein (DBP) is considered a carrier for vitamin D in the blood. A group of chemical processes which are necessary to produce the active form of vitamin D , the first is hydroxylation occurs at the 25^{th} carbon (C-25) and the second at carbon 1 (C-1).],The major form of vitamin D that circulate in the body and the most credible index of it's status is 25-hydroxyvitamin D [25(OH)D3 which resulting from 25-Hydroxylation of vitamin D in the liver .(**Christakos et al .,2017).**The key enzyme for the processing of vitamin D to 25(OH)D3is CYP2R1 **(Brown and Razzaque, 2015).**,25(OH)D3 then is carried by DBP to the kidney where it is recognized by megalin, which is a transmembrane protein acting as surface receptor. In the proximal renal tubule, Formation of 1,25(OH)2D3, that is vitamin responsible for the biological properties of D is done by hyroxylation of25(OH)D3 by 25(OH)D3 1αhydroxylase (CYP27B1) **(Perwad and Portale,2014).**

1.3-Vitamin D deficiency and insufficiency : serum concentration of 25(OH)D is the best index for vitamin D status, while 1,25(OH)2D ,the active form of vitamin D, is not valid because it's half-life is short and it associates weakly with intake of vitamin D **(Marzolo and Farfán,2011).**To define

deficiency ,unique reference values of 25(OH)D are not present. Regarding The Institute of Medicine (IoM) ,25(OH)D levels >50 nmol/l for 97.5% of the population considered sufficient level, risk for inadequacy or deficiency comes with population having levels of 30–50 nmol/l or <30 nmol/l **(Braegger C et al .,2013)**.

1.4- Association between vitamin D, antiepileptic drugs: It has been more than thirty years since there was found relation between antiepileptic drugs (AEDs),vitamin D, and health state of the bone in children diagnosed as epileptic (**Souvereinet al.,2006).**A lot of AEDs were found to have ability to induce the metabolic state of the hepatic CYP450 enzyme . As a result they elevate metabolism of vitamin D occurring in the liver, this will make the turnover of the bone occur rapidly than normal. However, other AEDs which don't have inducing enzyme criteria (e.g. valproic acid) were found to affect health state of the bone **(Guo C-Y et al .,2001)**.,Another new generation of AEDs (e.g. lamotrigine, levetiracetam, oxcarbazepine) are not necessarily indeclinable in bone metabolism, in spite of their minimal efficacy in inducing hepatic enzymes than carbamazepine or phenytoin **(Tekgulet al .,2006).**

Childhood Epilepsy

2.1-Definitions

Epilepsy: a brain disorder characterized by predisposition of production of epileptic seizures which will have outcomes psychologically, neurobiologically ,socially ,and cognitively. The occurrence of at least one epileptic seizure is necessitated to define epilepsy ***(*EngelILAE2001*).***

Epileptic seizure: signs and/or symptoms occur transiently secondary to activity in the brain neurons which occurs abnormally, synchronously and excessively ***(*EngelILAE,2001*).***

2.2- Epidemiology:-Worldwide10 · 5 million children below 15 years corresponding to 25% of the all epilepsy population were found to have active epilepsy, and more than 80% of them live in developing areas. In developed countries numbers in the first year of life represent 150 per 100 000 then reduce to 45–50 per 100000 after the child reaches 9 years. Up to the age of 15 years, 1· 0–1· 7% of children will have one unprovoked seizure at least, and 0· 7–0· 8% recurrent seizures this was proved by Cumulative incidence studies **(Forsgren 2004).**

2.3- Aetiology and pathophysiology

1-Genetic and molecular basis:- Epilepsy is known to be caused by mutations of single genes; however different phenotypes can be the result. On the contrary, different genotypes can result in identical phenotypes. Variability in phenotypes as assumed to occur due to modifier genes or determining the phenotypical expression by polymorphisms, environmental

factors also play role**.(Berkovic SF, Scheffer IE2001**).

2-Abnormalities of cortical development and neurocutaneous disorders:-A spectrum of epilepsy phenotypes appointed by Generalized epilepsy with febrile seizures plus including febrile seizures and febrile seizures plus. Febrile seizures plus associated with absence or myoclonic seizures, focal seizures, myoclonic a static epilepsy, and Dravet's syndrome were found to be less common phenotypic variations **(Singh et al .,2001)**.At least 40% of drug-resistant childhood epilepsies are attributed to the cerebral cortex malformations .Genetic mutations were found to have a link with some malformations and counseling regarding these genetic mutations is now available forlarge number of population **(Barkovichet al .,2005).**

3-Cerebral palsy :-epilepsy is found in children with cerebral palsy ,in quadriplegia and hemiplegia represents 50% in and in spastic diplegia and in dyskinetic CP represent about26%**(Hadjipanayiset al .,1997).**

4-Seizures and epilepsy following acute brain injury

Post-traumatic seizure occurring early , usually within 24 hour in about 3–10% of children with injury in the head. minortrauma in the head will be presented by early seizures and this have a good prognosis ,however late seizures may not be treated at all. The greatest risk will be found if there were depressed skull fracture, edema in brain , Focal neurological signs, and subdural haematoma **(Farrell K2004**).

2.4- Diagnosis of childhood epilepsy

The main diagnostic tool in epilepsy is good history taking. Cohesivesequele of manifestations be should gathered, regarding to age and status of the central nervous system. Developmental criteria should be included, if there was history of intake of any drug, and the family seizures' outcome. Zooming on the initial ictal symptoms, signs and postictal event, circumstances, and precipitating factors should be included when we describe the epileptic fits . comparing attacks should be the responsibility of parents as well as usage of videotape recordings at home. To clinically examine epileptic children we should make neurological, dermatological, and ophthalmological assessment and measuring the circumference of the head. EEG could detect abnormalities occur paroxysmally. Inspite that, depending on EEG at first for diagnosis is not a good idea , because abnormalities ofEEG occurring interictally were found in5–8% of non epileptic children **(Metrick et al .,1991).**The positivity index of EEG done routinely can be enhanced by sleep EEG from 60% to 90% **(Tassinariet al .,1998).** Photic stimulation that done intermittently, hyperventilation as well as video-EEGcould be necessary in children with epilepsy **(Stephenson,1999).**

Genetic TESTING

1-Microarray Analysis: Analysis of chromosomal microarray (CMA) was available for genome- wide analysis Since the early 2000s.techniques of CMA use probes of nucleic acid to detect changes in copy-number throughout the genome **(Vlaskamp et al. 2017).**

2-Gene Panelling: after EEG and neuroimaging for early onset epileptic children lacking any dysmorphic features, targeted next generation sequencing panels are the most cost-effective test could done initially **(Lindy et al. 2018).**

3-Exome Studies: they are comprehensive tests examining DNA variation which encode protein. In spite that, regarding epilepsy exome studies have interfering diagnostic product with gene panels **(Wang et al. 2014).**

Structural neuroimaging

1-CT:- It is indicated for assessment the sequle of head trauma associated by seizures or if there is emergent cases such as status epilepticus .

2-MRI:- is most reliable procedure, however children with typical idiopathic epilepsy and non complicated febrile seizures do not need imaging. **(Yetkinet al .,1998).**

Functional neuroimaging: Single-photon emission computed tomography (SPECT) is complementary in locating an epileptogenic zone. It involves usage as substrate of technetium-99m hexamethylpropylene amine oxime (99mTc-HMPAO) ortechnetium-99m-ethyl cystein at ediethylester(99mTc-ECD) to evaluate regional changes in cerebral blood flow during both the ictal and interictal periods.**(Wirrell 2010).**

2.5- Different epilepsy typesand response to treatment:-

1- Epileptic syndromes and focal epilepsies: Idiopathic focal epilepsies are the most frequent epilepsy syndromes in children. Age is a determinant of their course and may be found in several members of the family. They show good response to antiepileptic but it isn't sure if there is change in the outcome by treatment or not. Stoppage of the treatment is usually accepted by parents if they were told that the disease is self-limiting and there will no damage in brain. Carbamazepine or sodium valproate, are described if there is a need for treatment **(Bouma et al .,1997)**.

2-Benign epilepsy of childhood with centrotemporal spikes: includes 8–23% of epilepsy in childhood**.** Onset of seizure onset occurs from 3 to 13 years.**(Parmeggiani et al.,2004).**Typical seizures can lead to induction of sleep with contraction on face, difficulty in speach, dribbling, and a grunting, with intact consciousness. Unilateral upper limb is affected sometimes. Generalized convulsions can occur secondarily. Typical biphasic centro-temporal spikes are seen on EEG , with a tangential distribution when done interictally , which at sleep time become bilateral, we

can often avoid antiepileptic treatment **(Berg et al .,2003).**

3- Focal symptomatic epilepsies: represent 40% of epilepsy types (**Silva et al.,1996).** Monotherapies with valproate or carbamazepine are effective and tolerated well in newly diagnosed children as focal epilepsy whether associated or not with generalization that occurs secondarily to this focal type **(French et al .,2004).**

4-Idiopathic generalized epilepsies: primarily seizures can be generalized myoclonic, absence, and tonic-clonic. Responding to antiepileptic treatment is common but shows specificity according drug type .In 80% of patients Valproate show efficacy **(Guerrini et al .,1998**).

The International League designed Against Epilepsy (ILAE) has released a version at 2017 of seizure-type classification Some seizure types, for example tonic seizures or epileptic spasms, can have either a focal or generalized onset. Lack of information about the onset makes a seizure unclassifiable**.(FisherRS et al.,2017).**

Conclusion: Insufficiency and deficiency of vitamin D are highly prevalent among children with epilepsy. A lot of antiepileptic drugs lower vitamin D level and lead to more seizures specially enzyme inducers' drugs.

Table 1. Summary for the role of vitamin D in childhood epilepsy:

1- Vitamin D (VD) is considered a steroid that is active in neuronal cells and modulates the function and development of brain.	**(Groves et al.,2014).**
2- VD is involved in several processes of brain that include neurotransmission, neurotrophic factors regulation, immunomodulation of the nervous system.	.(**Jiang et al.,2014).**
3- A number of neuropsychiatric abnormalities are associated with low VD status and genetic polymorphism of vitamin D receptor (VDR)**.**	**(Eyles et al.,2013).**
4-Vitamin D proved to be involved in the development of epilepsy, there was significant association between VDR genetic variations and the risk of epilepsy in children especially temporal lobe type.	(**Pei Jiang et al,2015**).
5- Improving VD status can enhance the control of seizures in children with epilepsy**.**	**(Hollo et al.,2012**).
6-A lot of AEDs affect metabolism of VD and thus it's level by various mechanisms especially hepatic enzyme induction.	**(Guo C-Y et al .,2001)**

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