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Vitamin D Levels In Children Taking Sodium Valproate

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Abstract

Background: Seizures are a major cause of morbidity among the pediatric population and vitamin D is one of the most important micronutrients found in childhood. The interaction between valproate and vitamin D becomes a significant problem when faced in children with seizure problems.

Aim: The aim of the study was to see the effect of sodium valproate on the levels of vitamin D .

Design: Prospective case control study

Material and Methods: The study was conducted at the OPD of Department of Pediatrics, ASCOMS between August 2020 to December 2021. The study population consisted of 120 children among which 60 which have taken valproate for more than 6 months for seizures and 60 normal children as controls.

Results: Mean vitamin D levels at the beginning were nearly similar between case and control groups i.e. 49.57 ng/dl and 52.63 ng/dl respectively. At the end of 6 months of intake of sodium valproate , average levels of vitamin D was 24.32 ng/dl in study group as compared to the average levels of vitamin D 45.39 ng/dl in the control group.

Conclusion: The study identifies risk of vitamin D deficiency in children with epilepsy on sodium valproate. Vitamin D and calcium supplementation should be started with sodium valproate.

Keywords: Seizures, Vitamin D, Sodium Valproate

Introduction

A seizure is an abnormal paroxysmal electrical activity in the brain resulting in motor, sensory, behavioural or autonomic manifestations. About 5% of children experience a seizure in the first 5 years of life. (1) Seizure can also be defined as a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. (2)With the advancement in neuroimaging and a better understanding of the anatomy of the brain many attempts have been made to solve the mystery about what leads to seizures, but still the predictability of a seizure happening is low and most of them appear to be idiopathic. (3) Valproate remains the main drug in the management of childhood seizures as few drugs are developed in the last many years notably levetiracetam but the safety data available for valproate use is still far more than the new drugs which make valproate a reliable option for use in children. Vitamin D is one of the most important micronutrients in the diet of children as is linked directly with their skeletal development and deficiency in early life can leave a significant disability for the future. (4-5) Hence, the relationship between these two elements becomes essential to be studied. Although, the data regarding the interaction is present on a large scale but the data concerning our

region is lacking and this study tries to fulfil that void in the data.

Material and Methods

The study was conducted in the Department of Paediatrics, ASCOMS between August 2020 to December 2020 after getting ethical clearance from Institutional Independent Ethics Committee vide reference no. ASCOMS/IEC/RP&T/2020/381 dated 25th July 2020. The study population comprised of 120 children among which 60 children served as cases who fulfilled the criteria for epilepsy and were on sodium valproate. While 60 children of the same sex and age not taking any anticonvulsant served as controls. Data regarding the age, sex, type of epilepsy, and family history was from the caretaker accompanying the child. Vitamin D levels (25-(OH) D_3) was measured by the chemiluminescent method in both cases and controls before initiation of sodium valproate as well as after completion of 6 months of therapy. The results were recorded on a preformed proforma. Statistical analysis was done.

Exclusion Criteria:-

1. Children with kidney, liver, gastrointestinal disease, malignancy, cerebral palsy.
2. Children on vitamin D supplementation or having vitamin D deficiency.
3. Neonates.
4. Malnourished children.

Results: The mean age of cases (8.53)was 1.2 years more than the control (7.32) but had nearly the same standard deviation of 3 approximately. The age distribution had a p-value of 0.139 as shown in table 1.

Table 1. Age distribution in cases and controls.

	N	Mean (years)	SD	SEM	p-value
Cases	60	8.53	3.31	0.605	
Controls	60	7.32	2.92	0.532	0.139

The gender wise distribution of the study group has been shown in table 2 having p-value of 0.584.

Table 2. Gender wise distribution of cases and controls.

Gender	Cases		Controls		P-value
	No.	Percentage	No.	Percentage	0.584
Male	22	36.7	18	30	
Female	38	63.3	42	70	
Total	60	100	60	100	

The anthropometric variables of cases and controls are depicted in table 3. The p-value for weight and height were 0.122 and 0.128 respectively.

Table 3. Anthropometric variables of cases and controls.

Weight (Kg)	N	Mean	SD	SEM	P-value
Cases	60	19.8	4.42	0.825	0.122
Controls	60	18.1	3.84	0.701	
Height (cm)					
Cases	60	117.4	5.93	1.083	0.128
Controls	60	114.9	6.58	1.201	

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Pre-study levels measured represent that the difference between the mean of levels of vitamin D was not much appreciable between the cases i.e. 49.57 and controls i.e. 52.63, although, cases had a lower mean than the controls. The standard deviation was 9.52 and 11.23 respectively and SEM values of 1.738 and 2.050 in cases and controls respectively. The data of pre-study levels had a p-value of 0.259 as shown in table 4.

Table 4. Mean Vitamin D levels in cases and controls at the beginning of the study.

Vit D levels	N	Mean	SD	SEM	P-value
Cases	60	49.57	9.52	1.738	0.259
Controls	60	52.63	11.23	2.050	

Among the cases, 26 children had a decline in the vitamin D levels below 20ng/dl after the initiation of sodium valproate while only 8 children from the control population had a decline i.e. the decline was 3 times more common in the cases when compared with the control group. The calculated p-value had a magnitude of 0.021 as shown in table 5.

Table 5 Vitamin D reduction in cases and controls.

Vit D (<20ng/dl)	Cases		Controls		P-value
	No.	Percentage	No.	Percentage	
Yes	26	43.3	8	13.3	0.021
No	34	56.7	52	86.7	
Total	60	100	60	100	

Post-study levels represent a significant decline in the mean level of vitamin D in the cases from pre-study level of 49.57 to 24.32 which is more than 50% of the previous level. The values of standard deviation and SEM were calculated as 8.75, 9.83 and 1.638, 1.850 respectively in the cases and controls. The data had a p-value of 0.001 shown in table 5.

Table 6 Mean Vitamin D levels in cases and controls at the end of the study.

Vit D levels	N	Mean	SD	SEM	P-value
Cases	60	24.32	8.75	1.638	0.001
Controls	60	45.39	9.83	1.850	

Discussion

Seizure is a fairly common condition dealt in the pediatric age group and the main concern in the parents is regarding the future effect that the seizure will have on the development of the children. Vitamin D is referred as a hormone now due to the peculiar metabolism in the body as it involves three systems including the skin, liver and kidneys. Sodium valproate is an inhibitor of cytochrome which is needed for the conversion of vitamin D to an active form in the liver and hence due to the inhibition the levels of vitamin D fall on the long term therapy and hence, makes it important to supplement the vitamin in the children taking sodium valproate for a long time such as in epilepsy. Two mechanisms are suggested for inactivation of vitamin D by anticonvulsants, hepatic enzyme induction and activation of Pregnane X receptor (PXR) and Steroid xenobiotic receptors (SXR).All normal physiological adaptive mechanism in response to progressive 25(OH) D insufficiency and consequent secondary hyper-parathyroidism are promoted by this increased clearance .Hypovitaminosis D results in decreased calcium absorption from the intestines.(6-7)*Fatma et. al. and Maryam et.al.* both had a very similar mean ages of the cases and controls to our study population.*Fatma et.al.* had mean age of cases 9.6 years and controls 9.5 years whereas *Maryam et.al.*

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had mean age of 8.4 and 7.7 years respectively in cases and controls.(8-9) The study conducted demonstrates this fact as every second child had a significant decline of more than 50% in the 6 months of sodium valproate and while among controls only 13.3% population had a minor decline. Many studies have been conducted which support the outcome we encountered in our population *Xu et. al*. in their study has conducted a meta-analysis of eleven publication and reported that all of them saw a significant decline in the levels of the vitamin D in which children were put on sodium valproate for the seizure control.(10-14) In our study also, we came to a result that a significant p-value of 0.001 was achieved in the two groups. Such dramatic decline makes it essential to start therapy with vitamin D at the initiation of the treatment because of the central role of vitamin D in the development of our skeletal system .(15-16) This drug does affect the bone mineral metabolism adversely, as manifested by decreased vitamin D levels in serum of children taking sodium valproate. The daily requirement of vitamin D in an infant is 400 IU while in children >1yr is 600 IU.(17).In this study, a direct association can be established between the sodium valproate and vitamin D levels but the effect of sodium valproate on different isoforms of the cytochromes in the liver still need to be found to optimise the treatment for an individual and also, the qualitative and quantitative change in the other nutrients such as calcium needs to be evaluated on a large scale study. (18-21)Sodium valproate remains to be one of the most widely used anti-epileptic medications to be used among the paediatric group and also due to the excessive data available to support the safety, efficacy among the group is one of the strongest point in favour of usage of this drug. With advancing time new anti-epileptic are made having similar or better usage results but the data and the experience that has been gained with sodium valproate still needs to be evaluated and in near future, we can be well assured that sodium valproate is going to maintain its supremacy it holds.

Conclusion

The study identifies a significant risk of vitamin D deficiency in children with epilepsy on sodium valproate. There is a need of the supplementation of Vitamin D and calcium with the initiation of sodium valproate.

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