Vitamin D Levels in Children and Adolescents with Cerebral Palsy: Cross-sectional Study

Níveis de Vitamina D em Crianças e Adolescentes com Paralisia Cerebral: Estudo Transversal

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ABSTRACT

Aim: Tetraparetic Cerebral Palsy (TCP) patients may present risks factors for Vitamin D deficiency such as increased risk of malnutrition and possibly infrequent sun exposure. The present study aimed to compare the vitamin D status in this population of TCP pediatric patients (Case Group) and compare them with healthy children and adolescents (Control Group). Methods: The clinical data obtained were: gender, age, weight, height, nutritional status, consumption of vitamin D food sources, sun exposure and serum levels of vitamin D. Vitamin D deficiency was defined as 20 ng/mL or less of 25(OH)D; "insufficiency" was defined as between 21-29 ng/mL; "sufficiency" was defined as between 30-100 ng/mL.[1] Results: Sixty patients aged 3 to 20 years old were divided into two groups: the Control Group (n=30) and the Case Group (n=30) composed of

individuals with TCP. Vitamin D levels did not differ between groups; the mean levels were 26.65 ng/mL (SD: 10.51) in the Case Group and, 28.93 ng/mL (SD: 9.26) in the Control Group. Conclusion: There was no difference identified between vitamin D levels among TCP and control patients, and no relationship between risk factors and serum 25(OH)D levels was observed. Even though Brazil is a tropical country with abundant sunshine during most of the year, there is still a considerable number of individuals with vitamin D classifications of insufficiency and deficiency in our study (N= 34/60). This should be alarming for healthcare professionals who work with the pediatric population, which is a population at risk for the development of disability.

Keywords: Cholecalciferol, Neurological Disorders, Pediatric, Deficiency.

RESUMO

Objetivo: Pacientes com Paralisia Cerebral Tetraparética (PCT) podem apresentar mais fatores de risco para a deficiência de vitamina D, como aumento do risco de desnutrição e possivelmente exposição infrequente ao sol. O presente estudo teve como objetivo comparar o *status* da vitamina D nesta população de pacientes pediátricos com PCT (Grupo Caso) e compará-los com crianças e adolescentes saudáveis (Grupo Controle). Métodos: Os dados clínicos obtidos foram: sexo, idade, peso, altura, estado nutricional, consumo de fontes alimentares de vitamina D, exposição ao sol e níveis séricos de vitamina D. A deficiência de vitamina D foi definida como 20 ng/mL ou menos de 25(OH)D; "Insuficiência" foi definida como entre 21-29 ng/mL; e "suficiência" foi definida como entre 30-100 ng / mL.[1] Resultados: Sessenta pacientes com idades entre 3 e 20 anos foram divididos em dois grupos: Grupo Controle (n = 30) e Grupo Caso (n = 30) composto de indivíduos com TCP. Os níveis de vitamina D não diferiram entre os grupos; os níveis médios foram 26,65 ng / mL (DP: 10,51) no Grupo Caso e 28,93 ng / mL (DP: 9,26) no Grupo Controle. Conclusão: Não houve diferença identificada entre os níveis de vitamina D entre os pacientes com PCT e controle, e nenhuma relação entre os fatores de risco e os níveis séricos de 25(OH)D foi observada. Embora o Brasil seja um país tropical com sol abundante durante a maior parte do ano, ainda existe um número considerável de indivíduos com classificações de insuficiência e deficiência de vitamina D em nosso estudo (N = 34/60). Isso deve ser alarmante para os profissionais de saúde que trabalham com a população pediátrica, que é uma população de risco para o desenvolvimento de deficiência.

Palavras-chave: Colecalciferol, Doença Neurológica, Pediatria, Deficiência.

1 INTRODUCTION

Vitamin D deficiency is being recognized as a pandemic due to the volume of people affected by the deficiency and the number of illnesses generated or stimulated by such a deficiency.[2] Vitamin D deficiency/ insufficiency is reported in an estimated 1 billion people worldwide.[3,4] The mechanisms associated with increased production of vitamin D are exposure to ultraviolet rays, followed by food sources such as: milk and dairy products, oily fish like tuna, sardines, salmon, cod liver oil, as well as eggs (with yolk), mushrooms, and foods that are artificially fortified by their manufacture.[3,5] Thus,

exposure to the sun and the consumption of this kind of food is important to maintain adequate levels of the vitamin in the body.[3]

Children and adolescents with Cerebral palsy (CP) may have vitamin D deficiency[6,7] since they are at an increased risk of multifactorial malnutrition, including: swallowing disorders, decreased food intake, sitophobia (the fear of eating) and gastroesophageal reflux.[8,9] Moreover, the limited mobility of these individuals could potentially increase the difficulty for them to be exposed to the sun and the most affected forms of CP may be more exposed to malnutrition.[10] CP has several clinical presentations, and to classify them according to the extent and intensity of motor dysfunction, the gross motor function classification system (GMFCS) was developed by Brooks *et al.* [11] According to this scale, Level V GMFCS is comprised of patients who have extremely compromised automobility and are transported by a manual wheelchair. This occurs in 9 to 43% of cases, in which bilateral diffuse lesions occur in the pyramidal system, causing severe spastic tetraparesis; in this case it is call tetraparetic cerebral palsy (TCP).[12]

TCP patients may have seizure syndromes and use antiepileptic drug. Enzyme-inducing antiepileptic, such as phenytoin, phenobarbital, carbamazepine, may alter vitamin D concentrations as well as osteoblast function, which favors a decrease in bone mineral density.[13]

Maintaining satisfactory levels of Vitamin D is essential for health maintenance as previously described; therefore, identifying high-risk populations is essential to develop tracking and treatment measures to avoid hypovitaminosis D. [14] Moreover, it has been reported that brain dysfunction may be associated with reduced Vitamin D receptor activity since cholecalciferol acts as a neuroprotector[15].

Vitamin D has a fundamental role in the metabolism of phosphorus and calcium, and is essential for the bone health of infants, children, and adolescents. Therefore, sufficient amounts of serum 25 Hydroxyvitamin D (25 [OH] D) must be maintained to ensure healthy bone development for the population[16]. Low levels of vitamin D in children with TCP are related to increased bone fragility and possible non-traumatic fractures.[17] Usually, the calcium levels in these children are also significantly lower, and the levels of PTH and alkaline phosphatase are significantly higher when compared to the controls.[6]

The present study aimed to compare vitamin D levels in individuals with TCP and controls.

2 METHODS

This was a cross-sectional study, developed in a tertiary university hospital, at a state university in Brazil, during the period of February of 2015 until April of 2016. The research was approved by the Institutional Research Ethics Committee.

Sixty patients aged 3 to 20 years old were divided into two groups: the Control Group (n=30) and the Case Group (n=30) composed of individuals with TCP. The patients were attended at pediatric gastroenterology and neurology outpatient clinics, at the university hospital, and were invited to participate in the study if they met the inclusion criteria.

The control group was selected according to the inclusion criteria, the sample size reached 30 individuals because that was the number of children in the case group at the general pediatrics outpatient clinic present for routine consultations, aged 3 to 17 years old, with no reported diseases. Their parent/guardian must also have signed the informed consent form (ICF).

During the period in which the study was carried out, 54 patients with TCP were monitored at the pediatric service. The sample was collected by convenience. The 30 patients were included because they match the inclusion criteria: aged between 1 and 20 years and had a definitive diagnosis of TCP, established by a Pediatric Neurologist, according to the clinical signs demonstrated by changes in muscle tone (spasticity) and the region of the body affected by the paralysis[18]. Their parent/guardian must also have signed the ICF.

Exclusion criteria: patients who were diagnosed with genetic diseases, or had any disease that might affect intestinal, hepatic, or renal vitamin D absorption, and those who were already taking synthetic vitamin D supplements.

The variables observed were: serum levels of vitamin D, gender, age, weight, height, body mass index (BMI), consumption of vitamin D food sources (sardines, tuna, milk, dairy products, egg, beef liver and mushrooms), through the food frequency questionnaire[19]; food that was consumed more than 4 times a week was considered as frequent food consumption and less than 4 was considered not frequent. Sun exposure was evaluated by exposure in minutes per day regardless of the time of day and number of days of exposure.

To classify the BMI of TCP patients, the specific growth curves for children with Cerebral Palsy by Brooks *et al*. (2011)[11] were adopted; malnourished individuals were defined as those below the 5th percentile of BMI for age, eutrophic individuals were

between the 5-90th percentile and obese individuals were over the 90th percentile, as established in the original study. For the individuals in the Control Group, the BMIs were converted to age-adjusted and gender-adjusted standard deviation scores (Z scores) using the *World Health Organization* curve (WHO, 2007)[20].

For the Case Group we evaluated: nutritional pathway (by gastrostomy (GTT), by nasoenteric feeding tube (NFT), by oral feeding) type of diet offered (industrial or homemade), and the use of any antiepileptic drug.

The vitamin D levels were measured by the physiopathology laboratory of HC-UNICAMP, using a LIAISON® kit. Vitamin D deficiency was defined as 20 ng/mL or less of 25(OH)D; "insufficiency" was defined as between 21-29 ng/mL; and "sufficiency" was defined as between 30-100 ng/mL.[1]

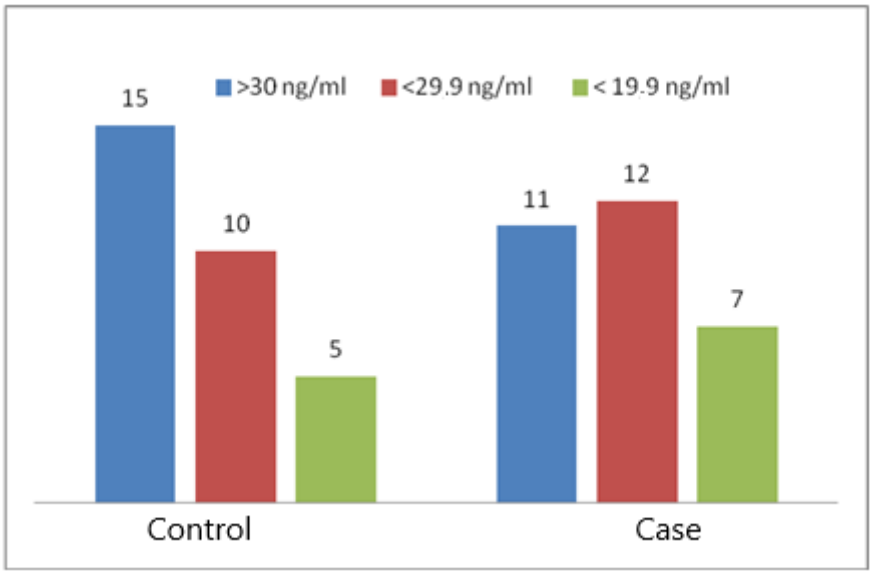
To compare the variables gender, sun exposure, nutritional status, and consumed food sources between groups, the Chi-squared test was used; moreover, when necessary, Fisher's exact test was used. Mann-Whitney and Kruskal-wallis tests were used to compare the age between groups and to assess vitamin D in relation to the variables gender, sun exposure, nutritional status, consumed food sources, and use of antiepileptic drugs. The level of significance adopted for the study was 5%.

3 RESULTS

The distribution of genders was 33 males and 27 females, of which 16 males and 14 females were of the Case Group, and 17 males and 13 females were of the Control Group. Ages ranged from 3 to 20 years old, with a median of 13 years (SD=4.34) in the Control Group, while in the Case Group the median was 11.5 years (SD=5.56). There was no statistically significant difference between groups in relation to age, demonstrating the comparability of the sample (p-value = 0.841).

Mean vitamin D levels were 26.65 ng/mL in the Case group (7 to 49.5 ng/mL and 28.93 ng/mL in the Control Group (11.9 to 50.4 ng/mL) and did not differ between groups (p-value = 0.333). Figure 1 presents data of Vitamin D level (ng/mL), classified as sufficiency, insufficiency, and deficiency (N: 34/60).

Figure 1 - Vitamin D distribution values between the case and control groups, classified as sufficiency (> 30ng/mL), insufficiency (<29.9ng/mL) and deficiency (<19.9ng/mL).



Vitamin D levels were not related to sun exposure in minutes per day regardless of the time of day (P-value Case Group =0.455; Control Group =0.377), number of days of exposure (P-value Case Group =0.916; Control Group =0.054), and exposure time (P-value Case Group =0.470; Control Group =0.766). The comparison between Case and Control Groups concerning gender and sun exposure with their respective p-values are shown in Table I.

Table I - Comparison of the Variables: gender, and sun exposure between the groups, and p-value of the association test among the variables.

Variables	N	Case (n=30)	Control (n=30)	P-Value
Gender				
Male	33	53.33%	56.67%	0.795
Female	27	46.67%	43.33%	
Has the habit of exposing themselves to the sun?				
Yes	44	70%	76.67%	0.559
No	16	30%	23.33%	
How many days a week of sun Exposure?				
At least 3 days	12	47.62%	26.09%	0.138
Everyday	28	52.38%	73.91%	
Daily Sun Exposure in minutes				
At least 15 minutes	13	28.57%	30.43%	0.969
Between 20 and 30 minutes	18	42.86%	39.13%	
Between 40min and 60 minutes	5	28.57%	30.43	

*Chi-square and fisher exact test.

Classification of nutritional status, type of nutrition and the type of diet received were analyzed in the Case Group. Sixteen individuals received a homemade diet through

the oral route or gastrostomy. These variables did not show statistically significant differences with the levels of vitamin D (Table II).

Table II - Case Group analysis: vitamin D levels, nutritional status, type of nutrition and diet type, and p-value of the association test between the variables.

Variables	N	Mean / SD	P-Value
Nutritional Status			
Malnourished	6	27.80 / 11.80	0.446
Eutrophic	24	24.92 / 8.41	
Type of Nutrition			
Gastrostomy	16	29.08 / 7.66	0.296
Oral	10	23.91 / 10.90	
Feeding Tube	4	23.74 / 18.69	
Diet type			
Industrialized diet	14	28.93 / 10.83	0.271
Homemade diet	16	24.65 / 10.13	

*Mann-Whitney and Kruskal-Wallis test.; SD – Standard Deviation

Concerning consumption of sardines, tuna, and bull liver, these vitamin D food sources were not consumed frequently in either group. Eggs were also not frequently consumed (1/16 in the Case Group and 7/30 in the Control Group). Milk consumption was the most common vitamin D food source (13/16 in the Case Group and 22/30 in the Control Group) (p= 0.722); followed by dairy products (7/16 in the Case Group 7/30 in the Control Group) (p= 0.189).

It was not possible to perform the statistical analysis for the use of Phenytoin, because only 3 patients used it, and none used Carbamezepine. Seven TCP patients used Phenobarbital, and their vitamin D mean was 23.7, SD=12.9 ng/mL (P-value =0.239).

4 DISCUSSION

In our study we found no significant difference between vitamin D levels among control and TCP patients. We also found no relationship between risk factors studied for vitamin D deficiency and serum 25(OH)D levels; however, we observed that many of the individuals studied were within the classification of vitamin D insufficiency and deficiency in both groups (N: 34/60).

We did not observe a difference in the vitamin D values between the female and the male genders. Nevertheless, in the study by Al-Ghannami *et al*. (2016), it was observed that vitamin D values were higher among young boys with a mean of 19.72 ng/mL, compared to 15.4 ng/mL seen in young girls (p <0.0001). Their findings may be due to the fact that the official religion of Oman obliges girls to cover their bodies more

than the boys, thus, they probably receive less sun exposure and have a consequently lower production of Vitamin D.[21]

Vitamin D levels mean were 26.65 ng/mL in the Case group and 28.93 ng/mL in the Control Group. The vitamin D levels found in our study are higher in TCP patients than those found in similar studies; such as a study conducted in 120 Indian children where median 25(OH)D levels of the CP patients were 14.2 ng/mL, and 24 ng/mL for the Control Group.[6] Another study was carried out in Finland with 44 children aged 9 to 18 years old with some type of motor deficiency diagnosis; of these, 40 had a diagnosis of CP. The median vitamin D level of the study was 17.6 ng/mL.[7]

In the present study we found a prevalence of malnutrition among 20% of the TCP patients, using the specific curve for the evaluation of this population[11]. Many factors are involved in the development of malnutrition in patients with CP. A survey was carried out in the Republic of Botswana among 61 CP individuals, and 26 of them (43%) met criteria for malnutrition. The main factors identified for malnutrition were severity of gross motor function and socioeconomic status. The higher the classification of GMFCS, the greater their need was to be fed by other people.[10] Perenc *et al.* found that the highest GMFCS level was linked to higher proportions of malnourished children, reaching 3.5 times higher in children with quadriplegia than in those with diplegia and hemiplegia.[22]

Identifying these patients at risk for malnutrition and proposing early treatment becomes essential for their growth, development and health.[23] In our study, we observed a smaller number of malnourished individuals, this may be associated with the fact that these patients are routinely monitored in a tertiary service, which promotes special attention to their nutritional status, since these are cases with greater neurological impairment. Regarding vitamin D levels, we also found no difference between TCP patients receiving a homemade or industrialized diet.

Milk consumption was the most common vitamin D food source, followed by dairy products in both Groups. This was contrary to the findings of the study by Neyestan *et al*. (2014) who observed a low acceptance of milk by Iranian schoolchildren. In a study with 374 Finnish children, the majority of the evaluated subjects did not consume the recommended daily amount of vitamin D.[24]

No relationship was found between vitamin D levels and sun exposure, nutritional status or type of nutrition in our study, nor was there any difference between sun exposure among control and TCP patients. Le Roy *et al.* also did not find any association between vitamin D levels and the other variables of their study such as nutritional status, GMFCS,

gender and feeding route. The patients studied had a high frequency of suboptimal vitamin D levels.[25]

This data differs from that found by Seth *et al.*[19], who observed greater sun exposure between control patients and the cases of those tetraparetic or non-tetraparetic CP patients. In Australia, a study looked at whether there were differences in vitamin D levels between different GMFCS classifications. Those that were within the GMFCS I to III groups had higher mean levels of vitamin D compared to GMFCS IV and V, but the difference was not significant. Therefore, higher levels of GMFCS did not emerge as a clear independent risk factor for vitamin D deficiency in the study,[26] as we also observed in our study.

In general, being exposed to the outdoors on days with longer periods of light helps to have higher levels of 25(OH)D[6,27]. Children with more motor impairment were expected to have less sun exposure. However, in the studied population this was not the case. Caregivers knew the importance of exposing the children to sunlight, probably because they are constantly exposed to proper information and medical professionals at the health facilities.

Phenytoin, carbamazepine, phenobarbital and primidone, which are inducers of the cytochrome P450 enzyme, are the antiepileptic drugs that are most commonly reported affecting vitamin D levels and bone health. In relation to the use of antiepileptic drugs, it was only possible to evaluate the relationship with vitamin D of those who used Phenobarbital due to the reduced number of those who used other medications. As a result, there was no significant difference between the vitamin D levels between users and non-users of Phenobarbital in TCP patients..[6]

As for the limitations of this study, it is possible to highlight the lack of evaluation of antiepileptic drug associated with vitamin D levels, which could not be determined by the low frequency in the studied group. In addition, the consumption of dietary sources rich in vitamin D, such as sardines, tuna, milk, dairy products and mushrooms, was not frequent enough in TCP patients to carry out statistical analyses.

5 CONCLUSION

No significant difference was identified between vitamin D levels among TCP and control patients. Unfortunately, we are not able to evaluate antiepileptic drugs associated with vitamin D levels, which could not be determined by the low frequency in the studied group.

Even though Brazil is a tropical country with abundant sunshine during most of the year, there is still a considerable number of individuals with vitamin D classifications of insufficiency and deficiency. This should be alarming for healthcare professionals who work with the pediatric population, which is a population at risk for the development of disability.

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