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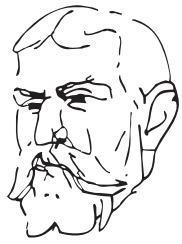

Memory of
dr Władysław
Biegański

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CONTENTS

ORIGINAL ARTICLE

VITAMIN D STATUS IN CHILDREN WITH PARALITIC SYNDROMS

DOI: 10.36740/WLek202309112

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ABSTRACT

The aim: Determination of serum 25(OH)D in the children with paralytic syndromes and its distribution depending on age, sex, taking anticonvulsant drugs, nutritional status for a period of one year (autumn-spring) of one center.

Materials and methods: There were recruited of 77 children with paralytic syndromes and 73 health children for the same period aged from 1 till 18 years. The study included a scrutiny of medical history and analysis of medical documents, assessment of motor dysfunction by GMFCS, and nutritional status.

Results: Among children with paralytic syndromes there were spastic tetraparesis 59.7%, malnutrition 92%, IV-V level of gross motor disfunction 80.5%, antiseizure medications 59.7% and cognitive impairment 77.9%. The variation of serum 25(OH)D is from 6.1 to 76.7 ng/mL with median 18.3 ng/mL in healthy children. The variation of serum 25(OH)D is from 2.2 to 83.0 ng/mL with median 14.8 ng/mL in children with paralytic syndromes (p=0.0103). Vitamin status among them is the following: insufficiency (21–29 ng/mL)–28.7% vs 16.8%; deficiency (<20 ng/mL)–56.1 vs 72.2% (p=0.0300). The 25.9% children with paralytic syndromes and those who have deficiency demonstrate severe deficiency (<10 ng/mL) compare 10.9% in healthy children (p=0.00189). There is a tendency to decrease of serum 25(OH)D in children with paralytic syndrome older 7 years.

Conclusions: We failed to record a significant difference in the 25(OH)D between males and females, between different level of GMFCS, and anticonvulsants using. Deficiency of vitamin D in 2.25 times higher in children with paralytic syndromes and severe malnutrition. Additional researches with specific items are need in perspective.

KEY WORDS: children, paralytic syndromes, vitamin D deficiency, COVID-19 pandemic

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INTRODUCTION

The thesis that millions of children may have suboptimal levels of vitamin D is formulated was confirmed in one national epidemiologic study of serum 25-hydroxyvitamin D (25(OH)D) in the USA pediatric population (ages 1-11 years): vitamin D deficiency is about 15%, and severe deficit up to 2% of the population [1]

Regarding the European population, the results of a meta-analysis of studies including 55,844 total participants, including 14,971 children (1–18 years), showed that 13 % European individuals had serum 25(OH)D < 30 nmol/L on average in the year. Strategies should therefore be developed to ensure vitamin D intakes that are protective against its deficiency in the majority of the European population. The prevalence of vitamin D deficiency and insufficiency varies significantly both in different countries and in different subpopulations of children depending on age and comorbidities [2].

Vitamin D is a hormone with a pleiotropic effect on many organs and tissues, and its deficiency plays role in the pathological mechanisms of many diseases. Among the pediatric population, low concentrations of serum 25(OH)D are associated with hypertension, obesity, metabolic syndrome, upper respiratory tract infections, vasculitis, chronic kidney disease etc. [3 - 8].

In 2011, Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline was published [9]. Firstly, the recommendations define Vitamin D deficiency is defined as a 25(OH) D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter). Secondly, determination of 25(OH)D in serum to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Conditions such as impaired motor function due to paralytic syndromes (cerebral palsy or other) are not identified in this document as indications for 25(OH)D measurement (candidates for screening). The document defines a group for screening - people who use antiseizure medications, which is possible in people with paralytic syndromes.

However, in 2017 European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children with Neurological Impairment recommend the mandatory determination of laboratory parameters for assessing the nutritional

status of children with neurological impairments, which include the study of serum 25(OH)D [10].

Since there is no clear definition of the risk group for developing vitamin D deficiency in children with paralytic syndromes and strong recommendations for screening of serum 25(OH)D in this group, we would like to contribute to clarifying this issue.

Hypothesis: in children with paralytic syndromes, the frequency of insufficiency and deficiency of vitamin D is higher than in healthy children.

THE AIM

Determination of 25(OH)D in blood serum in children with paralytic syndromes. Subobjectives: 1) compare serum 25(OH)D in children with paralytic syndromes and healthy children; 2) determination of serum 25(OH)D in children with paralytic syndromes and its distribution depending on age, sex, taking anticonvulsant drugs, nutritional status.

MATERIALS AND METHODS

Study design and setting. This study is single-centered (Rehabilitation Center with out-patient service), retrospective, case-control type. This study was performed for a period from October 2021 till March 2022 (autumn – spring seasons). We evaluated demographic and clinical data, determined the motor dysfunction, and assessed nutritional insufficiency.

Ethical approval. This study was approved by the Ethics Committee (The protocol № 5, date October 2021), which was conducted with the involvement of underage patients and did not contain measures that could harm their health. Both parents were informed about the methods and scope of the study and agreed to the participation of their children in this study.

Sampling. 150 children were involved in the study for one year period. The age of the children ranged from 1 to 18 years. Study group included 77 children with paralytic syndromes. Control group included 73 healthy children appropriate ages, who was recruited as volunteers from out-patient department with routine pediatrics observation and who had no any chronic and acute diseases during blood collection time.

Inclusion criteria: children 1 - 18 years with paralytic syndromes according to ICD - 10 (cerebral palsy G 80, hemiplegia G 81, paraplegia and tetraplegia G 82, other paralytic syndromes G 83) associated with CNS damage caused by hypoxia, bleeding, thrombosis, trauma; congenital brain defects.

Exclusion criteria: rickets-like hereditary diseases, undiagnosed progressive conditions with disorders of the central nervous system of unclear etiology, rickets in young children, congenital or hereditary skeletal disorders, liver and kidney diseases and those who were already taking synthetic vitamin D supplements.

Data collection**.** The study included a detailed scrutiny of medical history and analysis of medical documents, assessment of objective child' examination, anthropometric measurements and assessment by Gomez classification of protein – energy malnutrition [11], and movement disorders levels according to the GMFCS [12].

Determination of serum 25(OH)D (ng/mL) in children was performed by enzyme immunoassay on the analyzer "Labline-90" (Austria) using a commercial test system manufactured by Diagnostics Biochem Canada Inc. (Canada) according to the instruction provided. All 150 portions of blood serum were collected with serum storage in the freezer at -20°**C** for no more than one month. According to Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline, deficiency <20 ng/mL, insufficiency - between 21 and 29 ng/mL, and sufficiency >30 ng/mL were considered to evaluate the results of serum samples for 25(OH)D [9].

Statistical analysis was performed with the program MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; 2018). Descriptive analysis, odds ratio (OR), relative risk (RR) and the 95% confidence interval (CI) was determined. For all parameters, their distribution was checked using the Shapiro-Wilk test. For comparison of two independent groups the Mann-Whitney (MW) test was used. For comparing proportions, the Chi-squared test was applied. The difference in parameters was considered statistically significant at $p < 0.05$ and if 95 % CI excluded of «1».

RESULTS

Table I presents demographic characteristics of children with paralytic syndromes and healthy children.

The distribution of children by age group was equal between children with paralytic syndromes and healthy children except young children. Among both the preschool aged children prevailed, and every fifth child with paralytic syndromes lived in rural areas. Table II presents clinical data of children with paralytic syndromes.

Some significant states and comorbidities were prevalent in this cohort. So, 71 (92 %, p=0.0001) children had malnutrition and 62 (80.5 %, p=0.0001) of them had IV - V level of gross motor disfunction. More than half 46 (59.7, p=0.0001) of the children had convulsions and antiseizure medications as mono- or bitherapy (leveti-

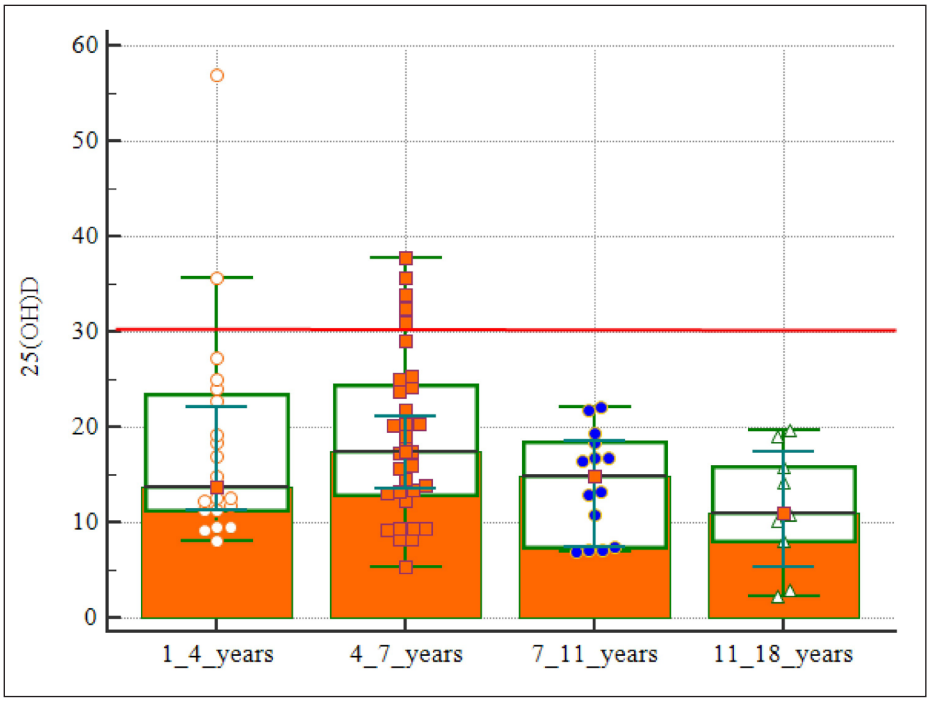

Fig. 1. Distribution of serum 25(OH)D depending on age in children with paralytic syndromes

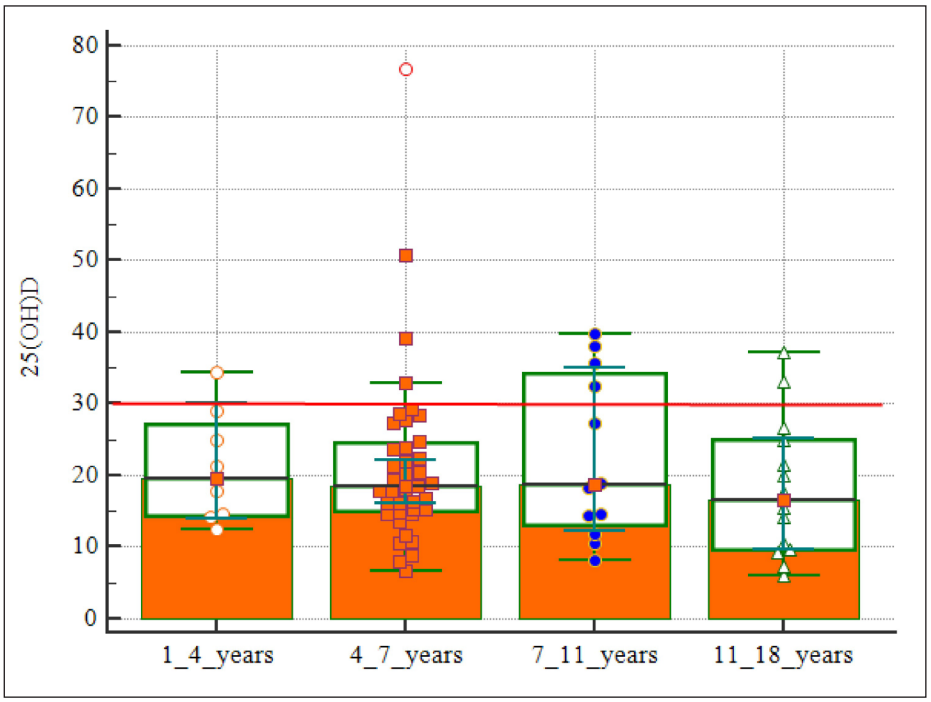

Fig. 2. Distribution of serum 25(OH)D depending on age in healthy children

racetam, carbamazepine, oxcarbazepine, clonazepam, valproic acid, gabapentin). 60 (77.9 %, p=0.0001) of the children with paralytic syndromes were mentally destroyed. Spastic tetraparesis was more common among the various types of paralytic syndromes - 50 (59.7 %, p=0.0035).

Table III demonstrates the medians, distribution and vitamin D status in total cohort.

There were significant differences between serum 25(OH)D in compare groups and a high proportion of vitamin D deficiency and severe deficiency among children with paralytic syndromes. The minimum value of 25(OH)D was 2.2 ng/mL in child with severe deficiency.

We did not obtain a significant difference when calculating the probability of two states of insufficiency and deficiency in children with paralytic syndromes compared with healthy children (OR=1.5, 95% CI 0.57 – 4.04, p=0.3915).

Another point of study was the assessment of the serum 25(OH)D in the children with paralytic syndromes depending on the sex, GMFCS level, protein – energy malnutrition, anticonvulsants using, and age.

Table I. Demographic data of children with paralytic syndromes

Data	Children with paralytic syndromes n=77	Healthy children n=73	p
Age, years Me [min; max]	5 [1.0; 17.5]	6.5 [1.0; 17.0]	0,7658*
1 – 4 years	20 (25.9)	8 (10.9)	0.0189
4 – 7 years	33 (42.8)	39 (53.4)	0.2220
7 – 11 years	14 (18.1)	12 (16.4)	0.7455
11 – 18 years	10 (12.9)	14 (19.1)	0.2368
Male abs., (%)	48 (62.4)	39 (53.4)	0.2713
Female abs., (%)	29 (37,6)	34 (46.6)	0.2713
Residents of rural areas	16 (20.7)	6 (8.2)	0.0260

*MW test

Table II. Clinical data of children with paralytic syndromes

Presentations	n (%)	95 % CI
	Category	
Spastic paraparesis	4 (5.1)	2.0 – 12.6
Spastic tetraparesis	46 (59.7)	48.5 – 69.9
Dyskinetic disorders	9 (11.7)	6.2 – 20.7
Double hemiplegia	18 (23.2)	15.3 – 33.9
	GMFCS	
II - III level	15 (19.4)	12.1 – 29.6
IV - V level	62 (80.5)	70.3 – 87.8
	Protein – energy malnutrition	
Mild	12 (15.6)	9.1 – 25.2
Moderate	6 (7.8)	3.6 – 15.9
Severe	53 (68.8)	57.8 – 78.0
	Complications and co-morbidity	
Mental retardation	60 (77.9)	67.4 – 85.7
Convulsions	46 (59.7)	48.5 – 69.9
Visual impairment	29 (37.6)	27.6 – 48.8
Skeleton deformations	16 (20.7)	13.2 – 31.1

Comparison of the serum 25(OH)D did not reveal any differences in the sex: 16.3 [min – 2.8; max – 83.0] ng/mL and 13.1 [min – 2.2; max – 33.9] (MW test, p = 0.3205) ng/mL respectively; between different level of gross motor disfunction II - III and IV - V level: 17.1 [min – 9.3; max – 56.9] ng/mL, and 14.5 [min – 2.2; max – 83.0] (MW test, p = 0.2193) ng/mL respectively; and anticonvulsant using or no: 15.7 [min – 2.2; max – 33.2] ng/mL, and 14.2 [min – 2.8; max – 83.0] (MW test, p = 0.9188) ng/mL respectively. Significant differences of the serum 25(OH)D were found in the children with paralytic syndromes who had severe malnutrition compare mild and moderate malnutrition: 13.3 [min – 2.8; max – 83.0] ng/mL, and 17.8 [min – 7.0; max – 56.9] (MW test, p = 0.0464) ng/mL respectively.

We found the interesting results on the distribution of serum 25(OH)D depending on age in children. Graphical analysis demonstrates a decrease in serum 25(OH)D in the children with paralytic syndromes, depending on the age of the child, in contrast to healthy children (Fig. 1 Fig. 2). The serum 25(OH)D less than 30 ng/mL completely presented in children with paralytic syndromes.

Summarizing the results obtained, using binary logistic regression and relative risk calculation, we identified the most significant factors associated with hypovitaminosis D. We compared of the relationship between vitamin D deficiency with some contributive factors as GMFCS I-III and IV - V level; moderate and severe malnutrition (Gomes classification), age > and < 7 years in children with paralytic syndromes. We have established a relationship of vitamin D deficiency with GMFCS IV - V level; severe malnutrition, and the age > 7 years, but only valid for the severe malnutrition (table IV).

Table III. 25(OH)D serum levels in children and its description

Index/Presentation	Children with paralytic syndromes n=77	Healthy children n=73	p
25(OH)D, ng/mL Me [min; max]	14,8 [2.2; 83.0]	18,3 [6.1; 76.7]	0,0103*
Sufficiency (> 30 ng/mL)	8 (10.3)	11 (15.0)	0.7394
Insufficiency (21 – 29 ng/mL)	13 (16.8)	21 (28.7)	0.0812
Deficiency (< 20 ng/mL)	56 (72.7)	41 (56.1)	0.0300
Severe deficiency (<10 ng/mL)	20 (25.9)	8 (10.9)	0.0189

*MW test

Table IV. Deficiency of vitamin D in children with paralytic syndromes

Presentation	RR	95 % CI	p
GMFCS IV – V level	1.0	0.6 – 1.7	0.9618
Severe malnutrition (Gomes classification)	2.25	1.1 – 5.0	0.0462
Age > 7 years	1.2	0.8 – 1.8	0.3223

DISCUSSION

In this single-centered case-control study, we report the serum 25(OH)D level and vitamin D status for one-year period (autumn - spring) in children with paralytic syndromes and in the healthy children attended our Center. Our intention here was to clarify the issue for the clinical approach and of serum 25(OH)D screening to determine vitamin D status in children with paralytic syndromes. We put forward the hypothesis that the children with paralytic syndromes had high frequency of insufficiency and deficiency of vitamin D than the healthy children. The selected group for the study as children with paralytic syndromes is justified by the fact that they have many predisposing factors for vitamin D deficiency. However, there is still no consensus for this category of children regarding screening and robust recommendations for vitamin D supplementation [9, 10, 13]

We have showed the median level of serum 25(OH)D was 14,8 ng/mL and vitamin D deficiency was in 72.7 %, and insufficiency in 16.8 % in the children with paralytic syndromes.

However, we have received unexpected for us data on the high incidence of vitamin D deficiency and insufficiency in healthy children: 56.1 % and 28.7 % respectively. The finding by our point of view, of a high frequency of vitamin D deficiency among healthy children is associated with the diversity of the frequency of this status among different countries and populations. We found different published data for vitamin D status in populations in literature. As we stated above, 15 % of children aged 1-11 years in the US population are in vitamin D deficiency and 13 % European population (children and adults) [1, 2]. At the same time, a later publication states the following rates of Vitamin D deficiency: in <20% of the population in Northern Europe, in 30-60% in Western, Southern and Eastern Europe and up to 80% in Middle East countries. Severe deficiency was found in >10% of Europeans [14]. A certain period of time has passed between these publications. And we do not exclude the contribution to the development of vitamin D deficiency of such factors as less sun exposure of children and the digitalization of society, as well as the COVID-19 pandemic and lockdown restrictions [15, 16]. Our study was conducted during the period of partial lockdown measures. Moreover, the quality of life in children with CP is severely affected due to limitations in daily life activities, for instance eating, drinking, bathing, dressing, limited range of mobility owing to erratic muscle tone, wobbly gait, uncontrolled movements, poor balance, and deprived social functioning [17]. A national study in France of thousands of disabled children from birth to 18 years old studied their quality of life during the quarantine due to COVID-19. Children with an average age of 9.5 years mostly had cerebral palsy (42%) or neuromuscular diseases (11%). Quarantines negatively affected morale (44% of children), behavior (55% of children) and social interactions (55% did not have contact with other children). A total of 44% of children stopped physical activity; 76% studied at home; only 22% continued medical observation [18]. Data on the positive effects of vitamin D for the prevention or treatment of COVID-19 in adults have been published, but it is still unknown whether vitamin D deficiency increases the risk of SARS-CoV-2 infection in children [19, 20]. No randomized trials have been conducted in the pediatric population.

We analyzed the clinical features and possible contributing factors of vitamin D deficiency in children with paralytic syndromes. The cohort of children was

characterized by a high incidence of spastic tetraparesis 46 (59.7%), cognitive dysfunction 60 (77.9%), severe motor dysfunction 62 (80.5%), using of anticonvulsant therapy 46 (59.7%), and severe malnutrition 53 (68.8%). The serum 25(OH)D was lower compared with healthy children, and deficiency and especially severe deficiency were higher than in the healthy children - 72.7 % vs 56.1 % and 25.9 % vs 10.9 %, respectively. Researchers have demonstrated different frequency of vitamin D deficiency and insufficiency in children with paralytic syndromes. So in one publication Vitamin D deficiency was present in **53.4%** of children with cerebral palsy versus **19.9%** in those without it [21]. At the same time, according to cross-sectional study, there were 47.8 % insufficiency and 30.4 % deficiency of vitamin D in children with cerebral palsy aged 2 to 21 years. The mean value of 25(OH)D was 24.3±8.8 ng/ml and all children had moderate and severe protein – energy insufficiency. Authors advocate the control of 25(OH)D levels and vitamin D medicines should be as equipped in rehabilitation and tertiary medical centers [22]. But studies were different in design and simples.

We failed to record a significant difference in the 25(OH)D between males and females as demonstrated by most studies.

The factor reported as a risk for 25(OH)D deficiency hepatic metabolism-inducing antiepileptic drugs through cytochrome P450. According to a systematic review and meta-analysis by found that pediatric patients on cytochrome P450 enzyme inducing antiepileptic drugs had statistically significant prevalence of vitamin D deficiency (OR 0.33, 95% CI 0.21–0.47). The antiepileptic drugs were categorized according to their effect on the cytochrome P450 system as inducers (carbamazepine, phenobarbital, phenytoin, topiramate, oxcarbazepine, and primidone), non-inducers (valproic acid and clobazam), or not metabolized by this system (levetiracetam, gabapentin, ethosuximide, vigabatrin, zonisamide) [23]. The authors noted the prevalence of vitamin D deficiency in 32% among them. However, the results of this review were based exclusively on children with epilepsy without motor dysfunction, excluding timing of anticonvulsant medications using.

The next special issue for discussion is the relation between vitamin D status and different level of the motor dysfunction. We did not get significant differences in vitamin D status when comparing children with levels II – III and IV -V by GMFCS. We found different published data in this research point. So, a significant correlation between 25(OH)D and GMFCS levels and related disorders such as epilepsy, mental retardation, dental problems and retention growth was demonstrated on a sample of 274 children aged 1-19 years old with cerebral palsy and a predominance of spastic tetraparesis (59.8%) [24]. Our research confirms the published result N Paker et al. [25]. We did not find a significant relationship between vitamin D deficiency and GMFCS IV – V levels. However, we have shown a trend towards a decrease in serum 25(OH)D in children with paralytic syndromes in children older than 7 years. Similar to our study, 119 children with paralytic syndromes, among whom spastic tetraparesis was in 88.3% with average IV level of GMFCS, no statistically significant correlation was found between vitamin D levels and gender, GMFCS, type of paralytic syndrome, season of the year and treatment with antiepileptic drugs. However, sufficient serum vitamin D levels were statistically significant in children with a mean age of 3.8 years, while children with a mean age of 6.4 years had low vitamin D levels [25].

Paralytic syndromes associated with the possibility of assimilation of a sufficient number of nutritional components due to impaired chewing, swallowing, motor disorders of the gastro-intestinal tract, etc. [10]. We found that vitamin D deficiency in children with paralytic syndromes occurs with severe malnutrition by 2.25 times (RR= 2.25, 95 % CI 1.1 – 5.0, p=0.0462). Nutritional assessment and feeding tube use, as well as clinical nutrition, should be the focus of the clinician's attention especially since are no established strong recommendations indicating which patients should receive a gastrostomy tube [26].

Considering that vitamin D deficiency or resistance is caused by one of four mechanisms: impaired vitamin D availability due to insufficient dietary intake, malabsorption disorders, or lack of sunlight (photoisomerization); violation of hydroxylation by the liver for the production of 25(OH)D; violation of hydroxylation by the kidneys with the formation of 1,25(OH)2D, and insensitivity of organs to vitamin D metabolites, we believe that monitoring and timely prevention of nutritional deficiency in children with paralytic syndromes is absolutely necessary for its prevention. Undoubtedly, questions arise regarding vitamin D supplementation for children with paralytic syndromes who receive balanced clinical nutrition

The strength of our study includes, we showed a higher incidence of severe deficiency in children with paralytic syndromes compared with healthy children, a decrease in serum 25(OH)D levels in children over 7 years of age, and a significant association with nutritional deficiencies. There were some inherent limitations associated with this study, firstly, the sample size. Our model was based on a retrospective single-center case-control study and was limited by time and number of patients. Secondly, there were very

few preliminary studies and research gaps regarding serum 25(OH)D in children with paralytic syndromes, and especially depending on the types of paralysis, which influenced the methodology of our study. Our study was limited to one autumn - spring season and took place during the COVID-19 pandemic. We were unable to assess whether there was an effect of different groups of anticonvulsants and of combined use in children with paralytic syndromes on serum 25(OH)D levels, which may undermine the strength of the study. A bias in the results of our general and subgroup analysis could be caused by the lack of data on the time of insolation of children and the study of the characteristics of their lifestyle. Finally, the origin and duration of vitamin D deficiency and insufficiency could not be elucidated. However, the results clearly deserve further study, increased data collection and improved quality of studies, especially across age groups with nutritional and lifestyle studies, in order to obtain more convincing data. Further studies are needed in our and other populations of children with paralytic syndromes to diagnose vitamin D insufficiency and deficiency and factors influencing them, both as predictors and as obligate markers.

CONCLUSIONS

1. The median level of serum 25(OH)D in children with paralytic syndromes is 14.8 ng/ml, that significantly lower than the median level of healthy children 18.3 ng/ml.
2. The vitamin status among them is as follows: deficiency (21 - 29 ng/ml) - 16.8%; deficit (<20 ng/ml) – 72.2%. 25.9% of children with paralytic syndromes and deficiency have severe deficiency (<10 ng/ml).
3. There were no any significant differences of the serum 25(OH)D in the sex, and level of motor dysfunction, and anticonvulsant using. But was a tendency to decrease of serum 25(OH)D in children with paralytic syndrome older 7 years. In this age category the serum 25(OH)D was no more than 30 ng / ml.
4. Significant differences of the serum 25(OH)D were found in the children with paralytic syndromes who had severe malnutrition 13.3 ng/mL compare mild and moderate malnutrition 17.8 ng/ml.

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