Nutritional status and use of enteral nutrition therapy in children and adolescents with central nervous system tumors

Estado nutricional e uso de terapia nutricional enteral em crianças e adolescentes com tumores do sistema nervoso central

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ABSTRACT

Introduction: Central nervous system tumors are the most frequent solid tumors in childhood. The disease and treatment have aggressive effects, with a high risk of malnutrition. Therefore, this study aims to evaluate the nutritional evolution of children and adolescents with CNS tumors, from the diagnosis through the sixth month of treatment. Methods: This was a retrospective cohort study conducted between 2020 and 2023. The nutritional assessment was done at the diagnosis moment (T0), after 30 (T1), 90 (T2), and 180 (T3) days of treatment, including weight, height and mid-upper arm circumference (MUAC) measurements. The study evaluated the motives for initiating nutritional support and the nutritional evolution according to the oncologic diagnosis. Results: Out of the 100 participants, 55% were male. The most prevalent diagnosis was medulloblastoma (24%). Significant statistical differences were observed on the body mass index or weight-for-age parameters (p=0,001) and the MUAC (p=0,028) throughout the study. The malnutrition prevalence according to the nutritional status classification and the inadequacy of MUAC was different between T0 and T3 (p=0.035 and p=0.034, respectively). Participants with medulloblastoma presented differences on nutritional evolution between the T0 and T3 (p=0,022), as well as T1 and T3 periods (p=0,036). Statistical difference was also observed when comparing the use of enteral nutrition therapy due to worsening of nutritional status and swallowing disturbances (p<0,01). Conclusion: Anthropometric data worsened over time and the prevalence of malnutrition increased. Nutritional care protocols need to be developed for these patients from the diagnosis moment, given the impact of the antineoplastic therapy on the nutritional status.

RESUMO

Introdução: Os tumores do sistema nervoso central (SNC) são os tipos de tumores sólidos mais comum na infância. A doença e o tratamento possuem efeitos agressivos, com alto risco de desnutrição. Assim, este estudo objetiva avaliar a evolução nutricional de crianças e adolescentes com tumores do SNC do diagnóstico ao sexto mês de tratamento. Método: Estudo de coorte retrospectivo acompanhado entre 2020 e 2023. A avaliação nutricional foi realizada no diagnóstico (T0) e após 30 (T1), 90 (T2) e 180 (T3) dias de tratamento, com aferição de peso, estatura e circunferência braquial (CB). Avaliou-se os motivos de indicação de suporte nutricional e a evolução nutricional por diagnóstico oncológico. Resultados: Dos 100 participantes, 55% eram do sexo masculino. O diagnóstico mais prevalente foi meduloblastoma (24%). Houve diferença estatística nos parâmetros de índice de massa corporal para idade ou peso para estatura (p=0,001) e CB (p=0,028) ao longo do estudo. A prevalência de desnutrição pela classificação do estado nutricional e inadequação de CB foi diferente entre o T0 e T3 (p=0,035 e p=0,004, respectivamente). Participantes comw meduloblastoma apresentaram diferença na evolução nutricional entre os períodos T0 e T3 (p=0,022) e T1 e T3 (p=0,036). Observou-se diferença estatística entre o uso de TNE por piora do estado nutricional e distúrbio de deglutição (p<0,01). Conclusão: Houve piora evolutiva dos dados antropométricos ao longo do tempo, com aumento da prevalência de desnutrição. É preciso elaborar protocolos de assistência nutricional para estes pacientes desde o diagnóstico, dado o impacto da terapia antineoplásica no estado nutricional.

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INTRODUCTION

Childhood and adolescent cancer, which affects children and teenagers from 0 to 19 years old, is a group of diseases that have in common the uncontrolled anormal cell proliferation and can occur in anywhere in the body. Most of them have unknown sources, 10% of them being associated to genetic or hereditary factors¹. Considered rare when compared to adult cancer², this type of disease represents the main cause of disease-related mortality among children and adolescents in Brazil. However, approximately 80% of the patients achieve cure if diagnosed early³.

The central nervous system (CNS) tumors are the second malignant neoplasm and the most prevalent solid tumor in childhood and adolescence and happen due to an abnormal proliferation of brain cells. Generally, these tumors correspond to 20% of malignancies, with the highest mortality rate being more incident between one and four years old⁴. In the Grupo de Apoio ao Adolescente e à Criança com Câncer (GRAACC), the CNS tumors represented 20,9% of all the new diagnosis in 2021⁵. The CNS signs and symptoms are nonspecific, although have a significant impact on children's life quality, such as low or no weight gain, growth deceleration, nausea and vomiting, among others⁴.

The illness itself and its treatment have aggressive effects, increasing the risk of nutritional compromise and malnutrition. The most common antineoplastic treatment modalities involve chemotherapy, radiotherapy, surgery and hematopoietic stem cell transplantation, depending on the type of tumor. Patients with low-grade gliomas usually undergo total tumor resection or a light conventional chemotherapy regimen as an adjuvant treatment or in the cases where the tumor removal is not possible. In the high-grade gliomas, partial resection of the tumor is commonly performed, followed by radiotherapy. Usually, complete surgical resection is the primary treatment of ependymomas associated with adjuvant radiation. The treatment of embryonal tumors, including medulloblastoma, pineoblastoma, atypical teratoid/rhabdoid and others, consists on maximal safe tumor resection, followed by craniospinal and bed radiotherapy, combined with intense systemic chemotherapy regimen. For individuals under 3 years old, the treatment focuses on high-dose adjuvant chemotherapy with autologous stem cell rescue to delay radiotherapy due to the risk of long-term side effects^{6,7}.

Pediatric oncologic patients may present some level of malnutrition at diagnosis and high incidence of malnutrition during the treatment as a result of the reduced food intake, increased energy expenditure, impaired nutrient absorption and other complications such as oral and gastrointestinal toxicity⁸. Pediatric patients with brain tumors may have risk of malnutrition throughout the treatment due to highly emetogenic chemotherapeutic agents, radiotherapy regimens and

direct damage to the musculoskeletal and nervous systems as result of toxicity⁹. In such cases, enteral nutrition therapy (ENT) is recommended for nutritional support. Additionally, the enteral nutrition (EN) can be recommended due to the development of dysphagia at diagnosis or following the surgical tumor resection. That scenario is commonly observed in children with posterior fossa tumors, because the neurologic structures of that area perform an important role in the efficiency and precision of the movements involved in deglutition¹⁰.

The nutritional assessment includes anthropometric, biochemical, clinical and dietary evaluations, and must be performed, since the diagnosis, directing the nutritional status of the patient and the appropriate dietary intervention¹¹. The World Health Organization (WHO) uses weight, height and BMI to classify the children's nutritional status according to age and sex through the growth curves, determining the appropriate z-score¹². However, those measurements may not be sensitive for all patients, since weight can be influenced by large tumor masses, hydration status due to fluid intake and organomegalies. In that case, the mid-upper arm circumference (MUAC) may be adopted as a complementary measure to evaluate muscle mass, available protein storage and lean body mass, being an easy, inexpensive and quick measurement¹¹.

The nutritional support through EN (nasoenteric tubes or gastrostomies) has shown significant results concerning the recovery and/or maintenance of the nutritional status. Currently, the early recommendation of enteral nutrition is one of the primary goals of nutritional therapy in children and adolescents with cancer. The main indications for ENT are mild malnutrition or weight loss between 5 to 10% with low oral intake for 3 to 5 days, severe malnutrition or recent weight loss above 10%, hypercatabolic scenarios, neurologic impairment and/or high risk of bronchoaspiration, including cases of dysphagia, mechanical pulmonary ventilation and respiratory failure^{13,14}.

Given the global impact of oncologic treatment in pediatrics, it becomes important to develop studies that assess the malnutrition rate among children and adolescents undergoing CNS tumors treatment, as well as understand the use of nutritional support in these patients. In light of the above, this study aims to evaluate the nutritional progression of children and adolescents with CNS tumors at diagnosis until the sixth month of treatment, while associating the anthropometric parameters with the CNS tumors subtypes and the justification for indicating ENT according to the study time points.

METHOD

This was a retrospective cohort study examining the followup and associations between the anthropometric variables and enteral nutrition therapy in pediatric patients with CNS tumors admitted between January 2020 and February 2023. The project used data from the study titled "Nutritional monitoring and assessment in children and adolescents with malignant neoplasia". The study was conducted at the Pediatric Oncology Institute of GRAACC, in partnership with Federal University of São Paulo. The research project was approved by the Ethics Committee under the protocol CAAE 48004921.1.0000.5505.

In the research, children and adolescents with diagnosis of CNS tumors admitted by the nutrition service who properly followed the standard nutritional care and monitoring service protocol were included. Exclusion happened in cases in which patients had unconfirmed cancer diagnosis, refused to provide their data for the study and presence of any condition unrelated to cancer that might interfere with the assessments and its results.

Data were collected through the medical records of participants from January 2020 to August 2023, covering a period of 6 months after the nutritional admission. According to the eligibility criteria, data from 100 participants were included.

The nutritional assessment was performed at diagnosis (T0), after 30 (T1), 90 (T2), and 180(T3) days from the nutritional admission. A 15-day margin was utilized, either before or after, to collect data according to the established period. Information on whether patients needed enteral nutrition therapy (yes or no) and the principal indication for the use was extracted from the participant's medical record.

For the present study the following variables were considered: sex (male, female); age (0-4 years, 5-9 years, \geq 10 years); coverage plan (Unified Health System - SUS, private health insurance); oncologic diagnosis (ependymoma, high-grade glioma, low-grade glioma, medulloblastoma, other embryonal tumors, germ cell tumor, choroid plexus tumor); use of enteral nutrition therapy (yes, no); justification for ENT use (dysphagia, nutritional status); weight (in kilograms); height (in centimeters) and arm circumference (in centimeters).

The anthropometric evaluation consisted in measuring weight, height and MUAC, described as follows:

- Weight: measured with a digital scale, with a capacity of 150 kg and 50 g precision to assist in nutritional diagnosis.
- Height: measured through a stadiometer, the patients were positioned vertically, standing upright, with shoulders and hips touching the wall. The feet were fully in contact with the floor, in a parallel position.
- MUAC: measured with a graduated tape measure, after identifying the midpoint between the acromion and the olecranon.

The nutritional status was evaluated according to WHO growth curves. To calculate the z-score, applications

developed by WHO¹² were used, in order to simplify the use of the reference curves for children from 0 to 5 years old (Anthro) and from 5 to 19 years old (Anthro Plus). The anthropometric indices adopted, in z-score, were weight-forlength to classify children who were up to 5 years old, and BMI-for-age to classify children and adolescents older than 5 years old. The nutritional status categories were malnourished (z-score \leq -2) and non-malnourished (z-score >-2). The MUAC was according to sex and age, using the classification proposed by Frisancho¹⁵, in which patients with an MUAC below the 5th percentile were considered inadequate.

To describe the sample, categorical data were presented in absolute numbers (n) and relative percentages (%). The symmetry of continuous variables was evaluated using the Shapiro-Wilk test. For variables with an approximately normal distribution, the mean and standard deviation were calculated. For those without, the median and interquartile range (IQR) were reported.

The association between nutritional status, MUAC and the variables sex, age, and oncologic diagnosis was examined using the chi-square or Fisher exact test, as appropriate, on each evaluation period. The McNemar test was adopted to compare the prevalence of malnutrition in different periods, using the nutritional status classification and MUAC inadequacy.

To investigate the possible differences in the evolution of anthropometric parameters throughout the treatment, the repeated measures ANOVA was employed for parametric variables and Friedman test for the non-parametric ones. The homogeneity of variances was checked using Levene test and, when necessary, Welch correction was applied. The sphericity of repeated measures was assessed through Mauchly test, with the Greenhouse correction applied as appropriate. Bonferroni post-hoc analysis was used to identify significant differences between specific groups after the overall analysis of variance. The adopted significance level for the analyses was p<0.05.

RESULTS

During the study period, 259 patients were admitted in the reference center with tumors in central nervous systems. From those, 139 patients, of both genders, matched the inclusion criteria established for this research. Thirty-seven participants were excluded because they had only one nutritional assessment at T0, making it difficult to observe the nutritional evolution during the treatment. After a preliminary data analysis, two patients under investigation for genetic and/or endocrine disorders were excluded, due to the possible impact on the anthropometric variables. Therefore, the data of 100 patients were selected for the final analysis.

The sample included 55 male participants (55%), with an average age of 5,9 years (SD \pm 5,16 years) and the majority

covered by SUS (80%). The most prevalent oncologic diagnosis was medulloblastoma (24%), high-risk gliomas (22%) and low-risk gliomas (18%). The complete demographic data can be observed in Table 1.

When analyzing the anthropometric data at different periods, differences were observed in height, BMI-for-age or weight-for-age indices, height-for-age index and arm circumference (Table 2).

At the initial assessment, malnutrition prevalence was at 8%. At T1, this rate was of 7.2%, while at T2 and T3, the rate increased to 18,7% and 22,7%, respectively. The nutritional status evolution, according to two different criteria (z-score

classification of BMI-for-age or weight-for-age and MUAC), during the different time points of the study is presented in Table 3.

Differences were not found in nutritional status (malnourished or non-malnourished) or in MUAC adequacy (below 5th percentile or above 5th percentile) between boys and girls or among the age categories at any time points of the research (data not shown). Figure 1 illustrates the evolution of BMI-for-age or weight-for-age z-score means for each oncologic diagnosis.

Regarding the evolution of each subgroup related to the clinical diagnosis, it was observed that patients with

Table 1 – Demographic characterization	of the sample.		
		n = 100	Percentage (%)
Sex	Male	55	55.0
	Female	45	45.0
Age (years)	0 to 4 years	50	50.0
	5 to 9 years	27	27.0
	10 years or above	23	23.0
Oncologic diagnosis	Medulloblastoma	24	24.0
	High-risk glioma	22	22.0
	Low-risk glioma	18	18.0
	Other embryonic tumors	15	15.0
	Ependymoma	9	9.0
	Choroid plexus tumor	8	8.0
	Germ cell tumor	4	4.0
Health Coverage plan	Public healthcare (SUS)	80	80.0
	Private health insurance	20	20.0

SUS = Unified Health System; n = sample size.

	Table 2 – Assessment of anthro	pometric data at different time	points; n = sample size
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	Diagnosis (n=100)	30 days (n=83)	90 days (n=75)	180 days (n=66)	р
Weight (kg)ª	18.0 (11.7-32.5)	17.25 (11.6-30.0)	17.65 (11.6-36.8)	18 (11.6-36.5)	0.962
Height (cm) ^a	109.5 (87.0-136.7)	105.5 (86.8-132.7)	110.0 (88.0-143.5)	110.0 (92.0-139.0)	<0.001°
BMI-for-age or weigh-for-length z-score ^b	-0.03 (1.39)	-0.09 (1.42)	-0.36 (1.78)	-0.65 (2.09)	0.001 ^d
E/I z-score ^a	0.03 (-0.92-0.77)	-0.13 (-0.83-0.47)	-0.45 (-1.20-0.41)	-0.62 (-1.42-0.30)	<0.001°
Arm circumference (cm)ª	17.2 (15.2-21.8)	16.7 (14.5-20.5)	16.5 (14.6-22.3)	16.2 (14.0-19.9)	0.028°

^a = median (interquartile range); b = mean (standard deviation); ^c = Friedman test (height: difference between T0-T2, T0-T3, T1-T2, T1-T3 and T2-T3) / (height-for-age: difference between T0-T1, T0-T2, T0-T3, T1-T3 and T2-T3) / MUAC: difference between T0-T3); ^d = repeated measures ANOVA, with Bonferroni post-hoc (difference between T0-T3 and T1-T3); n = sample size.

		n	Malnourished		Non-malnourished		
			n	%	n	%	р
Nutritional status (z-score IMC/I ou P/E <-2)	Diagnosis (T0)	100	8	8.0	92	92.0	
	30 days (T1)	83	6	7.2	77	92.8	1.000°
	90 days (T2)	75	14	18.7	61	81.3	0.118 ^f
	180 days (T3)	66	15	22.7	51	77.3	0.035 ^g
MUAC inadequacy (<5th percentile)	Diagnosis (T0)	92	4	4.3	88	95.7	
	30 days (T1)	80	6	7.5	74	92.5	0.625
	90 days (T2)	73	11	15.1	62	84.9	0.039 ^f
	180 days (T3)	66	16	24.2	50	75.8	0.004 ^g

Table 3 – Prevalence of malnutrition across time points (diagnosis, 30, 90, and 180 days) by nutritional status classifications and mid-upper arm circumference (MUAC).

^e = T0xT1; ^f = T0xT2, ^g = T0xT3, ^{*} = McNemar test; n = sample size.

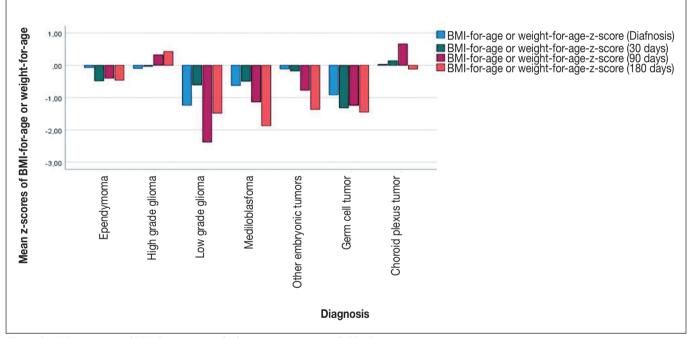


Figure 1. - Mean z-scores of BMI-for-age or weight-for-age over time, stratified by diagnosis

medulloblastoma presented difference in the nutritional evolution, measured by the BMI-for-age or weight-for-age z-scores throughout the period (F=7,83; gl (3,48); p=0,003; η^2 =0,118). Bonferroni post-hoc analysis revealed that those differences took place between the diagnosis and 180 days (t(16)=3,405, p=0,022), and between 30 and 180 days, respectively (t(16)=3,16, p=0,036).

Among all patients, 55 of them received enteral therapy nutrition. Those who required ETN due to worsened nutritional status (n=30) presented a decline in the mean anthropometric indices, while those who needed the enteral support

because of swallowing disorders maintained a stable mean during the study (F=8,461; gl (2,76); p<0,01; η^2 =0,158) (Figure 2).

To further investigate those differences, a Bonferroni posthoc analysis was performed. The results revealed statistically significant differences for the patients who required ENT due to worsened nutritional status between diagnosis and 90 days of treatment (t(37)=4,77; p<0,001), diagnosis and 180 days (t(37)=3,94; p=0,010), as well as 30 and 180 days of treatment (t(37)=3,96; p=0,009). These results are consistent with the hypothesis that nutritional evolution is influenced by the

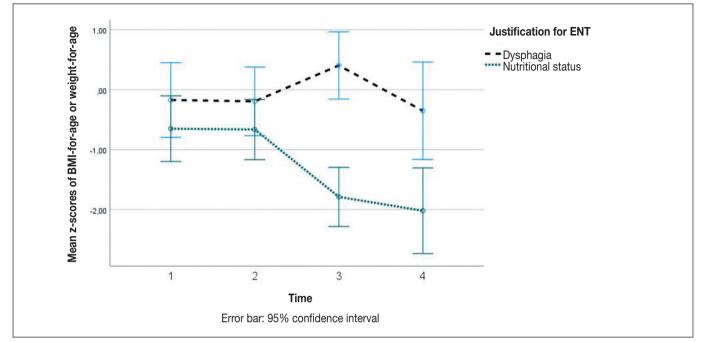


Figure 2. Nutritional evolution of patients according to the justification for enteral nutritional therapy use.

reason to initiate nutritional support, highlighting the importance of considering this variable when interpreting results.

DISCUSSION

Children and adolescents with cancer face the challenge of keeping sufficient dietary intake in order to maintain an adequate nutritional status while promoting growth and development throughout the treatment. Pediatric oncologic patients with poor nutritional status are at higher risk of complications during treatment and survival, including reduced life quality, higher relapse rates and mortality¹⁴.

According to Gallo et. al.¹⁶, who conducted a retrospective study evaluating the effect of nutritional risk screening and intensified nutritional support on treatment outcomes in pediatric solid tumors, it was observed that a negative impact on weight-for-height anthropometric index during treatment and the CNS tumor diagnosis were significant predictors of a less favorable survival outcome.

Corroborating with the present study, Zimmermann et al.¹⁷, in a study with pediatric oncologic patients that assessed the prevalence, occurrence and progression of malnutrition during the antineoplastic therapy, point out that malnutrition rates progressively increased over time. At diagnosis, 5,8% were malnourished, similar to the present study (7,8%), while 47% of the participants presented malnutrition by the end of the follow-up. In a cohort study that included 99 Canadian children diagnosed with cancer, 6% of the patients were malnourished at diagnosis moment¹⁸. These findings reinforce the idea that the increase in malnutrition after the start of antineoplastic therapy is associated with the intensive treatment protocols and the corresponding gastrointestinal side effects.

Besides, the same research demonstrates that patients with medulloblastoma, among all other oncologic diagnoses, are at higher risk of occurrence (94%) and time of malnutrition. Other CNS tumors presented 39% of malnutrition occurrence¹⁸. Meanwhile, in the present study, the malnutrition prevalence after 6 months of treatment was approximately 23%, with a 38% rate for patients diagnosed with medulloblastoma. The difference may be related to the follow-up time variation between both studies, being necessary to perform further studies to clarify the association. The cited study did not evaluate the nutritional intervention adopted for the participants.

Along with the numerous factors that contribute to the poor nutritional status, commonly seen in pediatric patients with cancer, children diagnosed with CNS tumors often exhibit factors resulting from the tumor's location and treatment. Patients with medulloblastoma, in addition to the low nutrient intake and absorption, may develop other side effects related to chemotherapy and craniospinal radiotherapy, leading to loss of appetite, anorexia, mucositis, chewing and swallowing complications¹⁹. This explains the important negative impact on the nutritional status in patients with that oncologic diagnosis, due to its intensive treatment, which justifies the weight loss during the treatment, especially in third and sixth months of monitoring, as a result of accumulated toxicity. Children undergoing medulloblastoma treatment in United Kingdom who used prophylactic enteral nutrition therapy, prior to the initiation of radiotherapy, whether by tube or gastrostomy, presented a smaller percentage of weight loss throughout the treatment¹⁹.

In the present study, there was a decrease in the MUAC median, and the inadequacy prevalence progressively increased over time. MUAC is a useful measure to be included in nutritional assessment due to its correlation with lean body mass, especially in patients who have extensive tumor masses that overestimate the body weight¹⁸. In a study evaluating nutritional status of pediatric oncologic patients and the association between the MUAC and length of hospitalization, arm anthropometric measurements demonstrated a higher prevalence of malnutrition when compared to the other anthropometric indices, in addition to showing a positive association with the length of hospital stay. Patients who presented an arm circumference below the adequate level were almost 2.73 times more likely to experience prolonged hospitalization²⁰.

Swallowing impairment has been reported as a symptom of brain cancer or a sequel after surgical removal of the tumor, mostly happening when located at the posterior fossa. The aspiration of food and/or liquids may be a result of dysphagia, leading to respiratory tract infections, increasing the risk of life-threatening complications for the patient. In severe cases, ENT is recommended as a safe feeding method²¹. In the present research, 55% of the participants required enteral therapy and those who needed ENT due to dysphagia had, on average, an adequate and stable nutritional status during the study. A study that analyzed the one-year outcome of post-surgical swallowing impairment in pediatric patients with posterior fossa brain tumor observed that 15% of the patients needed enteral tube feeding during the immediate postoperative period, while 6% continued using the ENT after one year after the surgical resection. Additionally, the use of enteral therapy for one year was significantly associated with involvement of the brainstem by the tumor, suggesting that the pathology and location of the tumor are risk factors for the prolonged use of enteral nutrition therapy²².

In the present research, those who required ENT due to impaired nutritional status had a significant decrease in the mean of anthropometric index after 6 months of treatment. The study performed by Bendelsmith et al.²³ analyzed the effects of proactive placement of enteral tube in children with high-risk CNS tumors who underwent aggressive treatment. Children who had used proactive enteral nutrition therapy showed consistent weight gain over the first years of treatment, while those who used ENT as a rescue after weight loss had an initial impairment in nutritional status followed by a recovery. Participants who were indicated for ENT and did not use it showed an initial impairment that remained without recovery. Furthermore, Kotch et al.²⁴ led a retrospective single-center study involving 26 children under 60 months of age with highgrade CNS tumors to evaluate the impact of proactive gastrostomy on comprehensive outcomes of chemotherapeutic treatment. Clinically significant weight loss was observed in 47% of the patients with nasogastric tube during induction, compared to 22% with proactive gastrostomy.

There are limitations of the present study that must be considered when interpreting its results. Firstly, the small sample size and the data loss during the research period may affect the precision of estimates and the generalizability of the results. Another limitation is that this study is single-center and retrospective. Additionally, the moment of ENT initiation, its duration of use, and the caloric-protein adequacy were not evaluated, making it impossible to compare the nutritional status evolution after the recommendation of this nutritional support method.

CONCLUSION

It is concluded that among the study participants, there was progressive deterioration of anthropometric data measured by BMI-for-age or weight-for-age and MUAC over time, with an increase of prevalence of malnutrition between the diagnosis moment and the sixth month of treatment. These findings are alarming due to the importance of adequate nutritional status throughout time, since children and adolescents who experience worsening anthropometric parameters are at higher risk for complications, with greater chances of relapse or mortality.

Therefore, it is of utmost importance to identify the malnourished patients or at nutritional risk in order to promote adequate growth and development for the child, reduce the risks of treatment toxicity and improve their life quality, through appropriate and specific nutritional support according to the child's needs.

Although the timing of indication, duration of use and dietary adequacy of the ENT were not evaluated, the participants who used ENT due to nutritional status impairments presented a significant decrease in the mean of anthropometric indices. Based on these findings, it is suggested that early and proactive enteral nutrition support may minimize weight loss and prevent nutritional decline after the initiation of treatment. This could reverse the findings of the present study. The need for careful monitoring of nutritional progression is crucial from the time of diagnosis, given the proportion of participants who used ENT due to worsening nutritional status.

Further studies in this area are needed to develop nutritional care protocols for these patients, especially those diagnosed with medulloblastoma, due to the impact of antineoplastic therapy on nutritional status and its importance throughout the treatment process.

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