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Malnutrition in Children and Adolescents with Cancer and the Challenge for Health Professionals: A Narrative Review

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Abstract:- Malnutrition in pediatric oncology is considered common, and this diagnosis may be underestimated according to the evaluation method. Causes of nutritional problems (malnutrition, overweight and obesity) are multiple and dynamic, and may vary according to different stages: diagnosis, chemotherapy, radiotherapy, surgery and treatment completion. Patients with some histological types of neoplasms such as carcinomas, bone tumors and lymphomas are more prone to malnutrition. Difficulties in the ingestion and absorption of nutrients can occur due to psychological causes, pain, mucositis, vomiting, nausea, dysgeusia and dysosmia. A relevant aspect is that nutritional status of cancer patients affects the intensity of symptoms, disease prognosis and quality of life, in addition to influencing the pharmacokinetics and pharmacodynamics of drugs used in antineoplastic therapy, with deleterious consequences in terms of effectiveness and safety caused toxicity. However, early diagnosis of malnutrition favors the use of nutritional supplements whose experiences described in the literature demonstrate effectiveness in children and adolescents with cancer. Real knowledge of the incidence of malnutrition may allow early initiation of preventive and therapeutic measures with an influence on the prognosis and quality of life of this special group of children and adolescents.

***Keywords*:-** *Malnutrition. Children. Adolescents. Malignant Neoplasms.*

I. INTRODUCTION

Malignant neoplasms in children and adolescents present different characteristics from those that occur in adult life, presenting a range of different malignancies, which may vary according to histological type, primary location of the tumor, ethnicity, sex and age. They are considered rare when compared to adult tumors, corresponding to between 1% and 3% of all malignant tumors [1,2].

Approximately 80% of children and adolescents diagnosed with cancer live in countries of low or medium socioeconomic development. In these regions, nutritional problems represent one of the main obstacles to effective cancer treatment, usually associated with late diagnosis, therapy abandonment and inefficient supportive care [3–5].

A study by AHOOCA (Association of Pediatric Hemato-Oncology of Central America) carried out in Central American countries showed that 45% of children had severe malnutrition at the time of cancer diagnosis [6]. In a systematic review study, 46 scientific publications on the influence of cancer and its treatment on the nutritional status of children were analyzed. Malnutrition rates ranged from 0 to 65%, however, the authors recommend caution in interpreting the results of this systematic review, as there was heterogeneity in methodology and definitions [7]. In another study that verified the nutritional status of 1154 children with cancer at diagnosis, malnutrition rates ranged from 10.8 to 27.3% depending on the method used, body mass index or triceps skinfold [8]

In pediatric oncology, causes of nutritional problems (malnutrition, overweight and obesity) are multiple and dynamic, and may vary according to different stages: diagnosis, chemotherapy, radiotherapy, surgery and treatment completion. Patients with some histological types of neoplasms such as carcinomas, bone tumors and lymphomas are more prone to malnutrition. Difficulties in the ingestion and absorption of nutrients can occur due to psychological causes, pain, mucositis, vomiting, nausea, dysgeusia and dysosmia [8–10].

A relevant aspect is that the nutritional status of cancer patients affects the intensity of symptoms, disease prognosis and quality of life, in addition to influencing the pharmacokinetics and pharmacodynamics of drugs used in antineoplastic therapy, with deleterious consequences in terms of effectiveness and safety. caused toxicity [11–13].

A study of 314 children with acute myeloid leukemia who received the same treatment protocol correlated body mass index with survival. Patients with overweight/obesity, malnutrition and adequate nutritional status had 5-year survival rates of 46%, 50% and 67% respectively. Patients with malnutrition showed a significant increase in the incidence of treatment-related mortality, especially infection (p=0.009) [14]. Similarly, studies with a small number of patients demonstrate the relationship between worse survival and nutritional impairment [15–18].

Protein-energy malnutrition increases vulnerability to infections, as it is associated with a decrease in the immune response and the protective function of the intestinal wall barrier [19,20]. In a study of 269 children with cancer, weight loss greater than 5% in the first three months of diagnosis was correlated with a higher incidence of episodes of fever, granulocytopenia and bacteremia. In addition, infections caused dose reductions or delays in the administration of chemotherapy with probable repercussions on the prognosis of the neoplastic disease [21]. In another study of 111 children with cancer, fever and neutropenia, the length of hospital stay was longer in malnourished patients [22–24].

However, the early diagnosis of malnutrition favors the use of nutritional supplements whose experiences described in the literature demonstrate effectiveness in children and adolescents with câncer [4] Therefore, the nutritional status of this population is an issue that should be included in the routine of therapeutic planning, but it is often not even identified early by health professionals [25].

One of the main obstacles to assessing nutritional status is the lack of standardized methodology. A study carried out by Maia-Lemos and collaborators [26] demonstrated that, considering the z-score values of the body mass index to identify malnutrition in cancer patients, the prevalence was 10.85%, however, when using other measures anthropometric measurements, such as triceps skinfold, arm circumference and arm muscle circumference, this prevalence increased from 10.85% to 27.02%, 24.74% and 13.83%, respectively.

A study conducted by Ferretti et al, with 1794 cases of children and adolescents with malignant neoplasms, showed that malnutrition was observed in 30.14% of the sample, considering classification by calf circumference, and in 13.3%, considering the BMI z-score [27].

These findings reinforces the idea that newer and more promising techniques should be developed in order to detect malnutrition earlier in patients with malignant neoplasms during treatment. [26]The interest in studies of anthropometric indicators to predict nutritional status lies in the need to establish reliable, easy-to-perform, low-cost techniques for early diagnosis of nutritional disorders and their consequences. Real knowledge of the incidence of malnutrition may allow early initiation of preventive and therapeutic measures with an influence on the prognosis and quality of life of this special group of children and adolescents.

II. MALNUTRITION IN MALIGNANT NEOPLASMS

The incidence of alterations in the nutritional status of patients with malignant neoplasms is controversial, ranging from 10 to 60%, according to the socioeconomic level of the population and the evaluation methods used. However, they represent concern for the health team, due to their clinical relevance, because regardless of the cause, the consequences will be deleterious, minimizing the therapeutic response, in addition to decreasing quality of life [7,28–32].

Children and adolescents with cancer are particularly vulnerable to malnutrition, as they have high nutritional needs due to the disease and treatment, in addition to the high demand for nutrients required to achieve adequate growth and neurological development. Malnutrition in patients with malignant neoplasms has consequent negative effects on clinical outcomes. Weight loss, especially the loss of lean body mass, is associated with higher morbidity and mortality, longer hospitalization time, due to reduced immunity, with a consequent increase in infections, impaired healing processes, muscle weakness, pneumonia, among other complications. deleterious, thus decreasing the patient's survival, in addition to increasing costs with this process [11,28,32–36].

Loeffen et al. [33], in a study that evaluated 269 children and adolescents under 18 years of age and aimed to assess whether malnutrition in the diagnosis of malignant neoplasm and during treatment would be prognostic factors for the rate of infection and survival, showed that the loss of weight greater than 5% in the first three months of diagnosis was related to episodes of fever, neutropenia, and bacteremia [odds ratio (OR) = 3.05, 95% CI = 1.27-7.30, p = 0.012].

In addition to clinical relevance, malnutrition also influences social and emotional aspects, which have been shown to be related to malnutrition in children and adolescents with malignant neoplasms. A study carried out by Brinksma et al [11] verified in 104 children and adolescents between 2 and 18 years of age with malignant neoplasms that, using a scale called HRQOL (lower health-related quality of life), malnourished individuals had worse physical, emotional and social, while those with adequate nutritional status had better HRQOL scores.

Unlike simple malnutrition, negative energy balance and muscle wasting in patients with malignant neoplasms are driven by combination of reduced food intake and metabolic disorders, such as high basal metabolic rate, insulin resistance, lipolysis and proteolysis, caused by systemic inflammation and catabolic factors. Malnutrition, in these patients, has a multifactorial origin, focusing on two aspects: metabolic alterations caused by the malignant tumor and adverse effects of anticancer therapy [29,32,33].

It is widely known in the scientific literature that early initiation of treatment is essential for better prognoses, however, the toxicity caused by it will result in inadequate nutritional intake, often observed in cancer patients and is associated with weight loss, which can be serious. For practical reasons, the ESPEN (European Society for Clinical Nutrition and Metabolism) disclosed in a Guideline [34] on nutrition in cancer patients, that inadequate food intake is considered present if it lasts longer than one week, or if estimated energy intake is less than 60% of nutritional requirements for one to two weeks. The causes of impaired intake are complex and multifactorial. Reduced food intake is caused by primary anorexia and may be aggravated by secondary deficiencies. However, early treatment of malnutrition and metabolic disorders caused by the disease are of great importance, for patients undergoing treatment and also for survivors [32,34]

The main secondary causes of reduced intake include chemosensory alteration, oral ulceration, xerostomia, dysgeusia, intestinal obstruction, mucositis, constipation, vomiting, diarrhea, nausea, reduced intestinal motility, among other alterations mainly in the gastrointestinal tract, responsible for food refusal, malabsorption and loss of nutrients, in addition to uncontrolled pain and side effects of drugs, thus contributing to the development of malnutrition and cachexia. Table 1 shows the main effects associated with chemotherapeutic agents commonly used in the treatment of cancer, which often lead to important changes in the patient's nutritional status [7,37–41].

The systemic inflammation syndrome, characterized by an intense pathophysiological network that promotes catabolic processes, is frequently observed in cancer patients, being associated with the development of fatigue, impairment in usual physical activity, anorexia and weight loss. The presence of malignant tumors causes metabolic and pathophysiological changes, being responsible for the release of inflammatory factors, which will affect the brain, muscle, liver and adipose tissue (Figure 1). Malignant tumor cells increase the production of proteolysis-inducing factor (increasing the loss of lean mass), pro-inflammatory cytokines, such as interleukins I and VI, and tumor necrosis factor, TNFα [32,34,42].

Table 1 Adverse Effects Associated with Chemotherapy Drugs Frequently Used in the Treatment of Malignant Neoplasms and Repercussions on the Nutritional Status of Patients

Adverse effect	Treatment	Nutritional effect
Nausea and vomiting	Most chemotherapeutic agents	May reduce food intake and cause dehydration
Anorexia	Most chemotherapeutic agents	Decreased appetite and food intake
Dysgeusia and dysosmia	CBP, cisplatin, DOX, cyclophosphamide, 5-FU, MTX	Reports of metallic taste of food, or intensely salty, sweet, bitter or sour, or even loss of taste
Diarrhea	5-FU, irinoteca, MTX, hydroxyurea, dactinomycin	Dehydration, loss of nutrients
Mucositis	Antimetabolites, cytotoxic antibiotics	Epithelial mucosal cells inflammation of the gastrointestinal tract
Stomatitis	Bleomycin, dactinomycin, DOX, 5-FU, MTX	Mouth injuries can affect food intake and cause food aversions
Metabolic changes	Cisplatin, MTX, mitomycin, tamoxifen, tretinoin, vincristine	Hypercalcemia, hypocalcemia, hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hypoglycemia, hypertriglyceridemia

CBP (Carboplatin), DOX (doxorubicin), 5-FU (5-fluorouracil), MTX (methotrexate) [34,39]

These cytokines affect the neuroendocrine control of appetite, causing anorexia and decreased caloric intake. A change in the metabolism of macronutrients is also observed, such as increased protein turnover, fat loss, loss of muscle mass and strength, increasing fatigue, in addition to an increase in acute phase proteins with, consequently, an increase in the basal metabolic rate, decreasing the clearance of the drugs used and increasing the toxicity of the treatment. Insulin resistance develops and glucose tolerance is reduced, energy stores in fat stores are depleted and, additionally, due to the action of cytokines, there is an increase in lipolysis and a defect in lipogenesis, a maladaptive and wasted response to the low consumption of food by the patient [34,37,43–51].

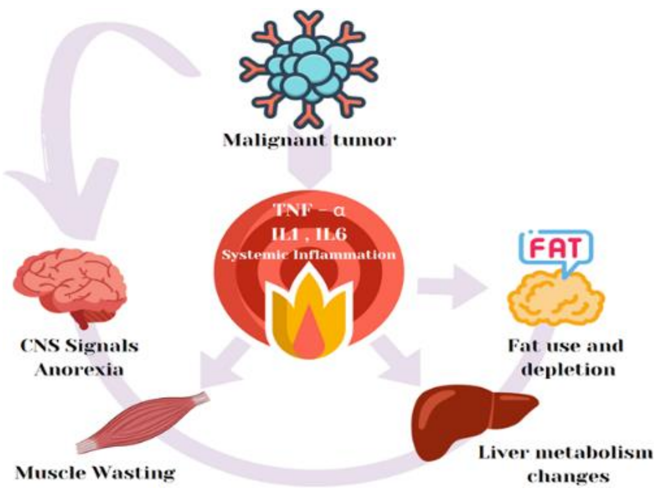

Fig 1 Metabolic and Pathophysiological Mechanisms for Malignant Tumor [32].

In fact, malnutrition is an independent prognostic factor in children with malignant neoplasms, in addition to being considered an important factor influencing survival. Muscle protein depletion is a hallmark of cancer cachexia, severely influencing quality of life and negatively affecting physical function and treatment tolerance. Studies on the body composition of cancer patients reveal that muscle wasting is specifically the main aspect of cancer-associated malnutrition that predicts the risk of physical impairment, postoperative complications, chemotherapy toxicity and mortality [15,16,34,52,53].

The biochemical alterations caused by the tumor and the toxicity imposed by the antineoplastic therapy will cause important alterations in the patient's nutritional status. However, this is a vicious cycle, as the presence of malnutrition will substantially influence the treatment, the need to reduce chemotherapy doses, increase the interval between chemotherapies, increase the risk of chemotherapy-induced toxicity, interruption of radiotherapy , increased postoperative complications and hospital stay, and impaired immune competence [39,41]

In addition, malnutrition will have consequences for the immune system in patients with malignant neoplasms. The hormonal and cytokine changes observed in response to malnutrition are closely linked to changes in immune cell populations. A study with malnourished children demonstrated that numbers of TCD4+ and TCD8+ cells were more reduced in whole blood compared to well-nourished children. In addition, childhood malnutrition causes atrophy of the primary lymphoid organs, leading to a reduction in the number of T and B cells and leads to the general state of leukopenia. These reductions in the number of immune cells in malnutrition contribute to functional deficiencies [51,54,55].

A well-established connection between systemic nutritional status and immune cell metabolism is through leptin, a hormone secreted by adipocytes in proportion to adipocyte mass and therefore is decreased in malnutrition. Leptin is best known for its role in influencing systemic metabolism, signaling the hypothalamus to increase appetite and decrease resting energy expenditure when body fat stores are depleted, as in malnutrition [49–51]

However, leptin acts directly on CD4 + T cells through the leptin receptor to direct changes in T cell metabolism and function. (77, 78) Because T cell metabolism and function are closely linked, any change in T cell metabolism and function immune cells can lead to a change in the function of that cell, altering cell proliferation, differentiation and cytokine production[20,55,56].

Malnutrition will also cause deleterious effects on the apoptotic function of mononuclear cells/neutrophils. Apoptosis, which refers to programmed cell death, plays an important role in the homeostasis of all tissues, including tumor tissue. Recent studies claim that apoptosis can explain the immune dysfunction observed in malnutrition. Apoptotic cells of the immune system can actively regulate the immune response, as well as extensive apoptosis can disrupt host defense and suppress the immune system [20,55,56].

Malnourished state is a common cause of secondary immune deficiency and an important risk factor for infection, sepsis and death, in addition to impaired immune response by reducing immunity, phagocytic function, secretory antibody response, and antibody affinity and affecting the complement and cytokine system. Therefore, apoptosis may explain the immune dysfunction observed in malnourished states [54–56]. A study that aimed to determine the effect of malnutrition on the apoptotic functions of phagocytic cells in 28 children with acute lymphoblastic leukemia (LLbA), 13 of whom were malnourished, found that the apoptotic functions of these patients, upon admission, were significantly lower than those of the control group . Among patients with LLbA, apoptotic functions were lower in patients with malnutrition than in those without malnutrition [56]. Repeated apoptotic functions of both LLbA groups were increased to similar values with the control group. This increase was considered statistically significant ($p<0.001$). After the dietary intervention, it was possible to observe an increase in functions in malnourished patients with LLbA. Thus, the importance of early identification of the state of malnutrition and rapid dietary intervention and implementation of nutritional support is emphasized, since malnutrition or cachexia lead to multiple complications, including for the patient's immunity [56] It is known that the success of the therapy employed is directly related to the nutritional status of the cancer patient. The loss of muscle mass and function is directly related to the increase in hospitalization time, hospital costs and higher mortality, especially in the case of a biologically very vulnerable group, in addition to being exposed to the aggressions of the disease itself and the effects of imposed toxicity by the treatment. On the other hand, studies show that, regardless of the length of hospital stay, early care reduces the risk of morbidity and mortality, slowing down the functional and physiological loss of muscle mass. In addition, a non-early diagnosis increases the chances of loss of muscle mass and function, leading the patient to a worse prognosis, both during hospitalization and after discharge [35].

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