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RESEARCH ARTICLE

Respiratory and Neuromuscular Impairment Resulting from Onco-Hematological Diseases and Treatment in Children and Adolescents: A Physiotherapeutic Approach

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ABSTRACT
Onco-hematological diseases are serious conditions and often require aggressive treatment that can lead to systemic complications, consequently affecting musculoskeletal functions as well as physical and functional capacity. Respiratory complications can lead to a greater frequency of hospitalizations and immobility, creating a cycle of sedentarism as well as an increase in morbidity and mortality. The goal of physical therapy in such cases is to restore compromised functions in affected children and adolescents and ensure the performance of activities of daily living and better development.The aim of this review was to bring to light the dysfunctions promoted by onco-hematological diseases of childhood in order to understand the best way to approach the treatment for this population.In this review, the functional alterations of sickle cell anemia, leukemia and bone marrow transplantation were addressed, as well as the interventions used by physiotherapy for the treatment.

Introduction

Systemic involvement is common in the diagnosis and recurrence of tumors and chronic hematological diseases as well as during or after the treatment of these conditions in the pediatric population. In many patients, pulmonary impairment can progress to rapid respiratory deterioration and death. All anatomic regions of the lungs may be involved, such as mediastinal structures, airways (trachea and bronchi), alveolocapillary units, pulmonary parenchyma, pleura, diaphragm and thoracic wall, leading to different functional impairments and, consequently, different rehabilitation approaches.[1] Identifying the dysfunction is the key to better treatment.

Pulmonary or cardiorespiratory changes can be primary, in which the initial involvement occurred in these systems, or secondary, in which these systems are impaired by treatments, immobility, pain, fatigue that go along with physical deconditioning, muscle atrophy, myopathy, sarcopenia, osteopenia, delay in neuropsychomotor development.

The physical therapist uses movement, manual techniques, physical instruments so that a dysfunction detected in the evaluation is rehabilitated or prevented. There are specialties that treat more cardiorespiratory disorders, whether primary or secondary; and neurological, however the performance ranges from the intensive care unit to outpatient and home sectors.[2,3]. The aim of this review was to bring to light the dysfunctions promoted by onco-hematological diseases (such as sickle cell anemia, leukemia, and bone marrow transplantation) of childhood in order to understand the best way to approach the treatment for this population within what exists in the current literature.

RESPIRATORY DISORDERS RELATED TO COMPROMISED ANATOMIC STRUCTURES

Pulmonary disorders can be divided into restrictive, obstructive and perfusion processes. Obstruction occurs in conducting airways and can be located in any region from the upper airways to the bronchioles, leading to hyperinflation as a consequence of the trapping of air.

Air trapping places the respiratory muscles at a mechanical disadvantage, especially the diaphragm, which becomes straightened, losing its effectiveness at generating volume and responding to increases in ventilatory demand. This situation is even more dramatic in the respiratory system of children, as the lungs have greater elasticity and the rib cage is much more compliant, which makes it insufficient to support the increase in demand in the occurrence of a reduction in inspiratory capacity [4,5]

The increased compliance causes the deformation of the rib cage when the respiratory muscles need to contract vigorously, leading to the emergence of retractions. Thus, signs of respiratory distress are quite evident and often emerge earlier in obstructive conditions compared to hypoxemia, which emerges as a result of hypoventilation and not due to a change in diffusion.

In restrictive processes, there may be a change in gas exchange area or changes in the rib cage whether due to infectious processes or non-infectious processes, such as a reduction in respiratory muscle strength and endurance, diminishing the capacity of the muscles to expand the lungs in an efficient manner. Diffusion is impaired a large part of restrictive disorders that comprise the region of the alveoli. Hypoxemia occurs early in such cases and often precedes signs of respiratory distress, as ventilatory inefficiency resulting from muscle weakness and thoracic restriction leads to hypoxemia secondary to hypoventilation [4,5].

Perfusion disorders occur when there is an obstruction in blood circulation, which can lead to pulmonary infarction, as can occur in sickle cell anemia and acute chest syndrome.

Thus, an understanding of the complications makes all the difference in the functional rehabilitation process for these children and adolescents.[6]

Skeletal muscle disorders and intolerance to physical effort are consequences directly related to respiratory disorders due the interdependence of these systems. Thus, physiotherapists need to perform a functional assessment to establish the best form of rehabilitation for these children and adolescents.

Sickle cell anemia

Definition, prevalence and incidence

Sickle cell anemia (SCA) emerges as a mutation in the bases that encode the sixth amino acid of the β chain of hemoglobin. A single nucleotide substitution of GTG to GAG makes the amino acid valine substitute glutamic acid in the protein chain. This altered translational event gives rise to a mutant variant of hemoglobin (HbS) with different properties compared to the molecule of wild-type hemoglobin (HbA). Under deoxygenation conditions, HbS molecules tend to aggregate in long rigid chains that distort the shape of erythrocytes, leading these cells to the characteristic sickle shape (polymerization). This sickling event continues to be the underlying cause of a set of clinical symptoms and complications.[7]

Sickle cell disease is the most common hereditary disease. An estimated 250 thousand children are

born with this disease throughout the world. The diagnosis is performed at birth using the foot test.

Clinical manifestations

There are no clinical manifestations at birth. Beginning at six months of age, there may be pallid cutaneous mucosa, jaundice, low weight/height gain and splenomegaly. At five years of age, there may be involution of the spleen (autosplenectomy) due to successive infarctions.

Pain attacks are the most common manifestations of SCA and the most frequent cause of hospitalization. Pain can be triggered by dehydration, changes in temperature, infection and psychological factors.

Acute chest syndrome (ACS) is an important cause of morbidity and mortality in SCA and is defined as an acute lung disease characterized by a combination of factors: chest pain, fever and a respiratory symptom (cough, tachypnea, dyspnea, bronchospasm, hypoxia) as well as new infiltrate in the chest x-ray. The cause may be infection, pulmonary vaso-occlusion or fat embolism.

Stroke can occur and is caused most often by stenosis of the internal carotid artery and middle and anterior cerebral arteries. Ischemic stroke is more common in childhood, whereas hemorrhagic stroke predominates in adulthood. Transitory ischemia can also occur and can cause neurocognitive damage, learning difficulties and a reduction in IQ.

Individuals with SCA are more susceptible to infections (pneumonia, osteomyelitis, urinary tract infection, sepsis and aplastic crisis) due to spleen dysfunction, tissue hypoxia and immune dysfunction[8]. (6)

Table 1. Associated chronic conditions[9]

-	**Growth and development** – delays in weight/height gain and sexual maturity.
-	**Cardiopulmonary changes** - cardiomegaly, left ventricular hypertrophy and pulmonary hypertension
-	**Kidneys**
-	**Ocular changes**
-	**Bone** – low bone mineralization, avascular necrosis of femoral head and expansion of bone marrow in maxilla and vertebrae
-	**Skin** – malleolar ulcers
-	**Hepatobiliary system** – hepatic infarction with abdominal pain

Functional changes

1. Acute

Pain – pain attacks should be promptly evaluated and treated with analgesia and hydration.

Acute chest syndrome – the patient normally needs to be hospitalized (most common cause of hospitalization in intensive care unit among these children) for treatment, which consists of ventilation, oxygen supplementation in cases of hypoxemia, intravenous hydration, analgesia, monitoring of ventilatory pattern, antibiotics, transfusion and bronchodilation in cases of bronchospasm.Maintaining an oxygen saturation above 94% is essential under these conditions.

An observational study conducted in 2018[10] found that obesity and obstructive sleep apnea are risk factors of invasive mechanical ventilation in these children during episodes of ACS.[11] Early noninvasive ventilation combined with routine transfusion is well tolerated in children with ACS and can avoid transfusion in some cases.

Some patients with non-pulmonary symptoms progress to ACS and evidence-based guidelines encourage the use of incentive spirometry for treatment.[12]

The study cited investigated the effectiveness of spirometry in the management of patients admitted with non-pulmonary disease to impede the development of ACS. The study not only showed a reduction in the occurrence of ACS in all patients, but also a statistically significant reduction in ACS in patients with pain in the back and no other respiratory symptom.

There is a possible overlap of SCA and asthma (15 to 28%), which is a factor that predisposes individuals to ACS. As expected with greater incidences of pain and ACS events, which are both independent risk factors for mortality, a diagnosis of asthma in individuals with sickle cell anemia is more associated with premature death compared to those without asthma. A prospective study involving children and adults with sickle cell anemia and two prospective studies involving adults with sickle cell anemia and sickle cell disease showed a link between asthma or recurrent wheezing and premature death.

These data show that a diagnosis of asthma or recurrent wheezing should be screened, detected and treated not only to prevent morbidity, but possibly also mortality. One of the greatest risk factors for future ACS is a history of a previous episode, particularly in children less than four years of age.[8]

The Peak expiratory flow rate (PEFR) studied in matched pairs of children with homozygous sickle cell disease revealed a highly significant reduction in PEFR of children with multiple episodes of acute chest syndrome when compared with those without. Similarly, measured forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and PEFR in SCA subjects were significantly lower than values obtained from non-sickle cell subjects.The effect of SCA on pulmonary functions becomes greater with increasing age and this has implications for the timing of commencement of treatment aimed at reducing chronic pulmonary morbidity in patients with SCA.[13]

Most children with SCA have lung function within normal limits, lung growth is significantly reduced compared to age- and race-matched controls. In adulthood, restrictive defects are commonly reported. Although these changes have already been verified in cohort studies at age below 11 years, spirometry is not indicative of predicting a reduction in lung function in adulthood, and the adult age of 32 years shows a relationship between these spirometric values as markers of early mortality. There is a gap that needs to be studied as well as a more sensitive assessment method in the age group below 11 years old that can predict this decline and association with mortality.[14]

2. Chronic

Reduction in physical capacity

Children with SCA have more adipose tissue and reduced physical fitness and exercise performance compared to control subjects. Resting energy expenditure is increased in children with SCA and may be associated with elevated markers of inflammation and oxidative stress. Lastly, pulmonary hypertension has emerged as one of the main causes of morbidity and mortality in adults and children with sickle cell anemia.[15]

Using the Six-Minute Walk Test, Liem and colleagues[16] and Campbell and colleagues[17,18] recently identified that the degree of anemia was the main factor that limited exercise capacity, together with restrictive lung function abnormalities and the number of ACS events.

Hand-foot syndrome – dactylitis

Hand-foot syndrome or dactylitis is characterized by acute ischemia of the bones of the hands and feet and is the first sign of pain in children. Vaso-occlusive events can begin in infancy up to two years of age and can have repercussions throughout life.[19]

The involvement of the osteoarticular system is very common, including conditions ranging reactive marrow hyperplasia to anemia and complications such as bone infarctions and infections. Although such events can occur in different organs, the bone marrow and epiphyses are the most affected. Bone infarction may manifest clinically as local pain, edema and erythema or may be asymptomatic. Fever and leukocytosis may also occur, but can complicate the differential diagnosis with infectious processes.[20]. This condition also contributes to a reduction in physical capacity.

LEUKEMIA

Cancer is a disease caused by a combination of hereditary and acquired changes in the genome. The DNA of neoplastic cells can alter normal growth and development processes. In children, tumors mainly affect blood cells and supporting tissues. In this specialty, the aim of physiotherapy is to preserve and restore the functional capacity of organs and systems and prevent disabilities resulting from the treatment to which the patient is submitted.

Epidemiology

In children and adolescents, the frequency of all types of cancer combined is generally higher in the male sex, children younger than five years of age and adolescents between 15 and 19 years of age. The main oncological diseases in children are leukemia (lymphocytic or acute myeloid), lymphoma (Hodgkin's and non-Hodgkin's), bone sarcoma, soft tissue sarcoma, retinoblastoma, neuroblastoma and central nervous system tumors.

Historically, children with cancer have been considered poor candidates for intensive therapy. Due to the bleak prognosis, admission to pediatric intensive care raises difficult ethical and operational issues. In recent decades, however, there has been an accentuated improvement in the prognosis of children with cancer (five-year survival increasing from approximately 40% in the 1970s to approximately 80% in the 2000s) as well as their results in intensive care.[21]

Clinical manifestations and functional changes

Common long-term effects of childhood cancer and its treatment lead to reductions in physical capacity, social integration and emotional wellbeing. The increase in survival rates underscores the need to minimize the adverse effects on physical capacity and reduce the impact of this growing morbidity on individuals, families and society.

The short- and long-term effects of chemotherapeutic agents such as vincristine and methotrexate can cause neuromuscular impairments that affect muscle performance. Medical treatment of hematological cancer can lead to neuromuscular impairments, including decreased neuromuscular activation, delayed onset of muscle contraction, reduced range of muscle activity, and decreased ability to generate muscle force. These treatments can also result in activity limitations in gross motor performance, including decreased balance, impaired coordination, and reduced movement speed and agility. The impairments of body structure and function and activity limitations in survivors of childhood leukemia go far beyond the completion of medical treatment .[22]

For all these reasons, physiotherapy becomes essential within this non-pharmacological context of the treatment of these children. Many deficits cannot be treated with medication and although they are crucial to sustain life, functional changes end up establishing themselves in chronic diseases during the course of treatment and can only be restored through rehabilitation measures.

Physical capacity is vital to child development and plays an important role in social participation. It is the capacity to use the musculoskeletal system to interact with the environment in a purposeful manner in order to perform activities of daily living and mobility. The adverse effects of cancer and its management often limit the motor performance and participation of affected children during treatment and survival.[23] Deficits can emerge as soon as the patient is diagnosed with cancer and can persist for years. The early identification of decline and establishment of an appropriate intervention is the key to maximizing physical functioning in children with cancer.

Side effects related to treatment, such as steroid myopathy, neuropathy, cardiotoxicity, nausea and fatigue, together with the loss of muscle mass and bone density related to prolonged hospitalization and psychosocial factors, are specific to children with cancer.[24]

Numerous pulmonary complications are related to cancer treatment, such as pneumonitis and fibrosis, which can compromise lung diffusion and capacity. Acute lung injury normally occurs as a result of the release of inflammatory cytokines in response to radiation, which leads to endothelial edema and perivascular lesions. Pneumonitis normally manifests as cough, dyspnea, hypoxemia and pleuritic pain. These symptoms emerge around 30 to 90 days post therapy. The main respiratory changes in children with leukemia are a reduction in inspiratory pressure and lung capacity (forced vital capacity and total lung capacity) as well as greater susceptibility to respiratory infections.

A cohort study[25] showed that children more than five years since diagnosis who were submitted to radiation have a greater relative risk of developing lung complications, such as fibrosis, recurrent pneumonia, persistent chronic cough, shortness of breath (due to the restrictive process) and rib cage abnormalities.[26]

Exercise prescription

The assessment of oncological patients should be daily and humanized, with the evaluation of neurological status, muscle tone, sensory system, cardiorespiratory system, gait and mobility. The goals of physical therapy are outlined based on the professional assessment with the aim of improving functioning and minimizing the sequelae of treatment.[3,27]

Table 2. Therapies and resources used for physiotherapeutic treatment of children with cancer[28] [13,29]

• Postural changes • Early ambulation • Aerobic exercises • Airway clearance • Lung expansion • Balance training • Toning • Strength exercises	• Adjustment of braces • Gait training • Kinesiotherapy • Manual therapy • Thermal-phototherapy • Virtual reality training • Play-based therapy • Inspiratory muscle training

Table 3. Precautions for exercise prescription [30,31]

Platelet count – 20 thousand or less – activities of daily living and passive exercises with considerable care; 20 to 30 thousand – free active exercises and walking with assistance for balance; 30 to 50 thousand – free active exercises, mild resistance
Hemoglobin – Hb < 8 – light exercise, isometrics, activities of daily living, avoid aerobics; Hb 8 to 10 – light aerobics, mild resistance, walking and observation of patient tolerance. Hb > 10 – resistance exercise, walking and observation of tolerance
Bone metastasis – >50% of cortex, do not perform exercise, do not use weight bearing exercises; 25 to 50% **–** active exercises and walking without traction and with partial weight bearing. 0 to 25% **–** light aerobics, avoid weight lifting and complete weight bearing.

There are barriers to the performance of physical exercise in cancer survivors, such as fatigue, an increased risk of infection, the side effects of treatment, pain, dizziness and weakness. There are also psychological and organizational barriers[21].

Reasons for admission to intensive care

The main reasons for admission to the pediatric intensive care unit (ICU) are sepsis and respiratory failure, which account for approximately two-thirds of non-surgical hospitalizations. Mortality is influenced mainly by the type of admission (surgical vs. non-surgical). Children admitted to the ICU in the postoperative period have a very low mortality rate (0 to 4%), whereas mortality in clinical cases is higher. A large multicenter study conducted by Dalton et al. demonstrated a 13.3% mortality rate of children with cancer admitted for non-surgical causes.

Like the general population in the pediatric ICU, the degree of failure of different organs is systematically related to the prognosis, as mortality exceeds 79% when three or more organs are involved. The use of mechanical ventilation and/or inotropic support related to respiratory problems and/or cardiovascular insufficiency are other important prognostic factors. The combination of these factors is associated with a poorer prognosis, with the mortality rate reaching 54 to 100%.

Children in the pediatric ICU at the time of the diagnosis of cancer (before the onset of chemotherapy) seem to have a better prognosis than those admitted later. This difference may be due to differences in the admission rates between these two groups and the toxicity of chemotherapy. Some authors also report that the type of cancer exerts an influence on mortality in the pediatric ICU: children with solid tumors have a lower mortality rate than those with hematological cancers.[21]

Noninvasive ventilation (NIV) is of particular interest in these patients, who are highly susceptible to infection, because it does not breach the respiratory barrier. The benefits of NIV for immunocompromised patients have been documented in adults and children.

In a retrospective study of 239 children with cancer in intensive care due to respiratory failure,[32] children ventilated for less than 24 hours with NIV (biphasic positive pressure in nasal airways) were compared to children on invasive ventilation. The success rate of NIV, which was defined as the absence of subsequent endotracheal intubation, was 74%. In the multivariate analysis, the predictors of NIV failure were cardiovascular dysfunction, therapeutic intervention, Therapeutic Intervention Scoring System (TISS score) ≥ 40 and presence of a solid tumor. Forty-six patients (39%) in the invasive ventilation group and 93 (77%) in the NIV survived to discharge from the pediatric ICU.[21]

Bone marrow transplant

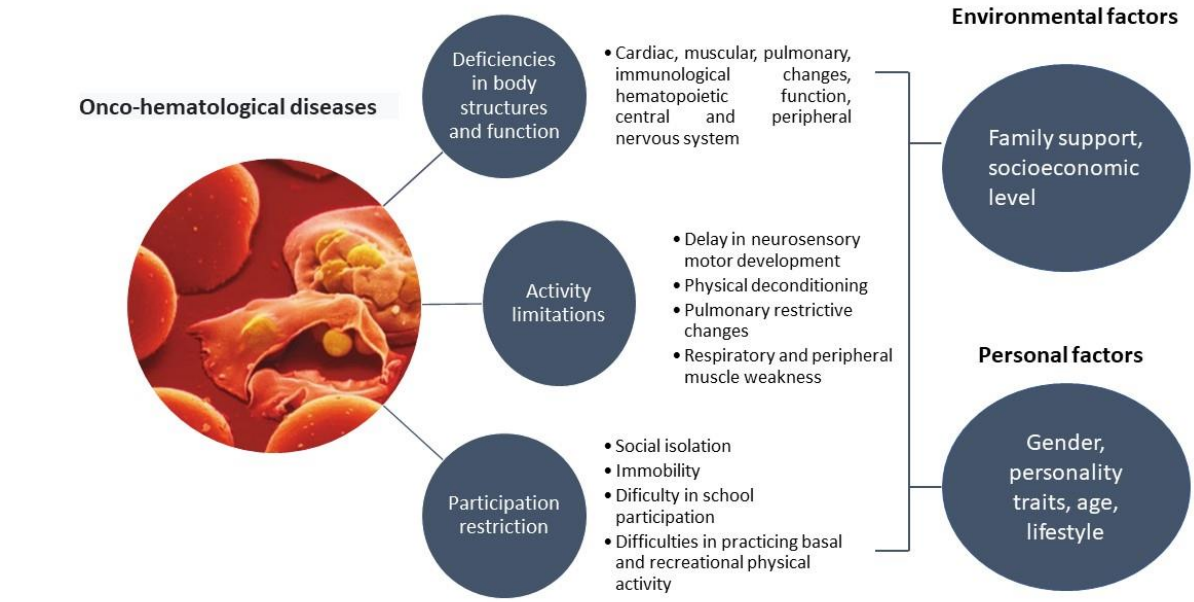
Hematopoietic stem-cell transplant (HCT) is a potentially curative therapy for pediatric patients with high-risk malignant diseases and non-malignant diseases. However, post-HCT pulmonary complications include infectious and non-infectious etiologies, such as idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH) and chronic graft-versus-host disease (GVHD)/bronchiolitis obliterans syndrome.[33,34]

Pulmonary complications occur in an average of 12% of pediatric patients. The one-year incidences include pneumonitis (8%), pulmonary hemorrhage (2%) and GVHD (2%). These complications can lead to a reduction in the survival rate in the year after diagnosis and are responsible for up to 16% of deaths following bone marrow transplants.[33]

The evaluation of physical rehabilitation after BMT dates back to at least 1986 and over time several studies have shown that patients involved in exercise programs require less physical support for activities of daily living and less dependence on

their caregivers for a large part of the time. . Health professionals are increasingly aware that patients awaiting BMT may present with several complex medical problems that directly impact their functional capacity[31].[22]

Fig 1. Summary of main disabilities, activity limitations, participation restriction and contextual factors



Physiotherapy

Physiotherapy is a health science that studies, prevents and treats intercurrent functional kinetic disorders in organs and systems of the human body, generated by genetic alterations, trauma and acquired diseases. It bases its actions on its own therapeutic mechanisms, systematized by studies of Biology, morphological sciences, physiological sciences, pathologies, biochemistry, biophysics, biomechanics, kinesis, functional synergy, and kinesis pathology of organs and systems of the human body and behavioral and social disciplines.

In children and adolescents during the period of hospitalization for the treatment of onco-hematological diseases, they often go through periods of isolation and reduced mobility, a situation that can lead to functional losses and motor delay depending on the age group. As a result of immobility on the bed due to treatment, these patients experience a reduction in costovertebral, costochondral and diaphragmatic movements, leading to a reduction in vital capacity and functional residual capacity, with a consequent reduction in expectorating capacity, which can lead to atelectasis and pneumonia. Thus, the goals of respiratory physiotherapy are (1) the prevention of respiratory complications (dyspnea, atelectasis, etc.), (2) bronchial clearance, (3) lung re-expansion, (4) assessment of respiratory work, (5) respiratory muscle training, (6) use of noninvasive ventilation when needed and (7) invasive ventilation support and weaning when necessary.[28]

Noninvasive ventilation can be used in both cases of respiratory failure and lung expansion therapy. Regarding physical exercise, studies and systematic reviews recommend aerobic and strength exercises for this population.[35,36,37]

Inspiratory muscle training (IMT) has been shown to be an efficient method of improving exercise tolerance and inspiratory and expiratory muscle strength in several diseases. Some studies have shown that IMT also increases the uptake of oxygen in the blood, decreases the perception of dyspnea and delays the onset of premature fatigue.[38]Incentive spirometry appears in studies for the prevention of acute chest syndrome as well as exercises with positive expiratory pressure with good results.[37,39]

The majority of studies separate chest physical therapy or physiotherapy from physical exercise[27] , which is not correct, since physical exercise is a strategy for the treatment and prevention of injuries to the patient who is confined, even within the list of interventions of respiratory physiotherapy, physical

activity [40]is implemented as a treatment and this terminology should change in studies in general.

Directions for the future

Although the knowledge for rehabilitative intervention in these children and adolescents is old, there is still not a robust body of evidence for recommendations[41] and the construction of a guideline.

The lack of evidence underscores the urgent unmet need for clinical trials in this area. In addition, the basis of the pathology in children with onco-hematological diseases has already made clear the importance of a multidisciplinary approach.

Conclusion

Onco-hematological conditions in children and adolescents are associated with numerous systemic dysfunctions that result from both the disease and the treatment to which they are submitted. The present review sought to show the look at multisystem disorders and possible non-pharmacological interventions within this context, as well as the particularities of this population at the time of adequate prescription of physical activity.

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