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CURRENT TRENDS IN THE CLINICAL APPROACH OF IDIOPATHIC SHORT STATURE IN CHILDREN: FOCUS ON GROWTH HORMONE THERAPY AND DIAGNOSTIC CHALLENGES

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Abstract: Objective: This literature review article addresses idiopathic short stature in children, highlighting the diagnostic complexity and the importance of personalized clinical and therapeutic approaches. Method: The research, which selected 15 articles between 2018 and 2023 in PubMed Central, highlights clinical assessment, involving anthropometric parameters, medical history and advanced exams, such as magnetic resonance imaging. Result: Growth hormone (GH) therapy is emphasized in the therapeutic approach, highlighting the importance of medication titration. Studies reveal improvements not only in physical growth, but also in psychosocial aspects in children undergoing GH treatment. Conclusion: Despite challenges in interpreting genetic tests, the conclusion highlights advances in clinical assessment. Although GH therapy is effective, issues such as titration and identification of ideal patients remain under discussion. The summary emphasizes the need for individualized approaches and points out gaps to be explored in future research, reinforcing the importance of a comprehensive and specific vision in the management of idiopathic short stature in children.
Keywords: Idiopathic short stature, Child growth, Growth hormone therapy.

INTRODUCTION

Hormonal short stature, also known as "idiopathic short stature", is an endocrine condition that has a direct and comprehensive impact on the physical development and height of children. It is currently one of the main challenges faced by pediatricians and pediatric endocrinologists in the country. This condition, whose prevalence has attracted increasing attention, is defined by clinical criteria that include a height less than the third percentile or more than 2 standard deviation scores (SDSs) below the mean in a sex- and

age-matched cohort (LEE et al., 2023).

To understand the etiology of short stature, methods are used that include a detailed anamnesis, a detailed physical examination and the study of the growth of living beings. Although notable advances have been made in the diagnosis of growth hormone (GH) deficiency, including genetic aspects and criteria for patient selection in genetic testing, the interpretation of these tests in the clinical context still remains challenging. This occurs, in part, due to controversies regarding the number of tests necessary to establish a conclusive diagnosis (PARTENOPE et al., 2022). In pediatric endocrine practice, children with short stature and no anomalies or dysmorphisms are divided into those with GH deficiency and those with normal GH levels (LEE et al., 2023). Furthermore, disagreements persist regarding patient selection, timing, dose and preparation of sex steroids, aggravating the complexity of the diagnosis.

The treatment of hormonally-related short stature in children aims to supplement the GH necessary to promote growth, metabolism and well-being. The initial dose of rhGH and subsequent adjustments are based primarily on total weight or body area and response to treatment. The objective is always to establish the lowest effective dose, which requires an individualized approach. In addition, research is underway with new treatment modalities, including long-acting GH formulas and new GH secretagogues. The importance of discussing hormonally-related short stature and its treatment in the scientific literature must not be underestimated, as children with short stature face not only a decrease in self-esteem, but also an increased vulnerability to verbal and physical abuse. Studies indicate, for example, that growth hormone (GH) therapy can have positive impacts on well-being during childhood and improved quality of life (SHEMESH-IRON et al., 2019).

Therefore, the main objective of this literature review article is to investigate the evolution of clinical assessment and therapeutic approach to short stature caused by hormones in pediatrics over time. Furthermore, we seek to identify and analyze the most effective strategies for early diagnosis and treatment of this condition. The purpose is to provide guidance for health professionals in the management of hormonally-related short stature in pediatrics, based on best practices and recent advances in the area.

METHODOLOGY

This literature review follows the criteria of the PVO strategy (population or research problem, variables and outcome). The research focuses on the evolution of clinical assessment and therapeutic approach to short stature of hormonal origin in pediatrics, with an emphasis on strategies for early diagnosis and treatment of this disorder. The population or research problem encompasses pediatric patients who suffer from short stature. The searches were carried out in PubMed Central (PMC) with the combination of the descriptors "Short Stature" and "Pediatrics" using the Boolean operator "AND". Initially, we identified 17 articles, which were subjected to rigorous selection criteria. The inclusion criteria covered articles in English, published from 2018 to 2023, and that were related to the research themes, including review and meta-analysis studies, as long as they were available in full. Duplicate articles, abstracts that were not directly related to the study proposal and those that did not meet the other inclusion criteria were excluded. As a result, we selected a total of 15 articles to compose this study. This rigorous approach aims to provide a comprehensive analysis of strategies for assessing and treating hormonally-related short stature in pediatric patients, with a focus

on the evolution of these practices over time.

DISCUSSION

CLINICAL ASSESSMENT

Within the scope of clinical assessment of child growth, it is imperative to compare the patient's development both with their individual standards and with those of the same age group, identifying potential early changes (LABARTA et al., 2021). The therapeutic perspective is based on improving quality of life, requiring a careful and increasingly evidence-based assessment of the benefits, risks, costs and value of treatment with human growth hormone (hGH) (GRIMBERG; ALLEN, 2017).

The clinical assessment begins with the analysis of anthropometric parameters, covering height, head circumference and medical history, including details about pregnancy, assisted reproduction, consanguinity, birth data and family history (COLLETT-SOLBERG et al., 2019). Even given the idiopathic predominance of this disorder, it is essential to investigate the clinical and family history, looking for possible justifications for growth impairment, such as genetic abnormalities.

When conducting the clinical evaluation of pediatric patients with short stature, it is imperative to investigate the underlying etiology of the disorder, based on auxological, anatomical and laboratory data (MAGHNIE et al., 2018). The diagnosis of growth hormone deficiency (GHD) remains challenging for the pediatric endocrinologist, demanding a comprehensive approach (PARTENOPE et al., 2022).

During the evaluation, it is crucial to consider other conditions that may influence failure to thrive, such as hypothyroidism, early or late puberty, as well as neurological symptoms. Suspicion of underlying diseases requires investigation through laboratory tests (COLLETT-SOLBERG et al., 2019). Collett-Solberg et al. (2019) highlight that cases, such as family short stature, female short stature or a history of childhood cancer, can be misinterpreted, particularly in female patients, requiring an assessment equivalent to that of men.

For additional investigations, LABARTA et al. (2021) suggest carrying out magnetic resonance imaging and computed tomography, aiming to identify intracranial tumors or structural or developmental anomalies. In cases of GH deficiency, it is crucial to evaluate the size of the pituitary gland, the anatomy of the peduncle and the position of the pituitary gland, and the use of gadolinium in magnetic resonance imaging has recently been considered unnecessary, especially in children due to potential harm.

The calculation of bone age, part of the clinical assessment, stands out for its ability to determine delays or advances in the child's development. However, in specific cases, such as obese children and those under two years of age, bone age can be altered without indicating growth abnormalities (COLLETT-SOLBERG et al., 2019). Advanced technologies, such as the software system for automated measurement of bone age from x-ray images of a child's hand, represent progress in calculation accuracy, although manual assessment is always necessary to rule out possible technological flaws (LABARTA et al., 2021).

The systematic review conducted by MAMELI et al. (2023) aimed to evaluate the efficacy and safety of long-acting growth hormone and growth hormone in children with growth hormone deficiency, concluding the absence of significant differences in both efficacy and adverse events.

Disorders associated with short stature can be categorized as primary, secondary

and idiopathic. The primaries are linked to the growth plate, including clinically defined syndromes, skeletal dysplasias and factors that result in small for gestational age (SGA) births (MAGHNIE et al., 2018). Cardoso-Demartini et al. (2019) highlight that the prevalence of SGA is higher in children born prematurely, especially those born less than 34 weeks. The Brazilian Society of Pediatrics (SBP) currently recommends clinical monitoring of growth in premature babies, considering the growth channel after stabilization of neonatal weight loss, with 10% of these children not developing adequately, contributing significantly to cases of short stature in adulthood.

Regarding secondary growth disorders, these alter the environment of the growth plate and include lack of growth hormone (GH), disorders of the GH-insulin-like growth factor IGF-I axis, endocrine and metabolic disorders, disorders of the organic, malnutrition, psychosocial disorders and iatrogenic conditions (MAGHNIE et al., 2018). Partenope et al. (2022) highlight that serum IGF-I and IGF-I binding protein type 3 values are useful biochemical indicators, while random serum GH concentrations have limited applicability, except for neonates.

Family medical history and targeted physical examination are crucial to rule out body disproportions and syndromic characteristics. A careful assessment of pubertal status complements the diagnostic approach (PARTENOPE et al., 2022). Brain magnetic resonance imaging is indicated to investigate hypothalamic and pituitary disorders, while hand and wrist radiography helps to analyze bone age, contributing to a more accurate diagnosis (PARTENOPE et al., 2022). After analyzing the selected articles, there is a lack of consensus on the ideal screening tests for evaluating children with short stature, highlighting the diagnostic complexity of this disorder.

THERAPEUTIC APPROACH

Within the scope of the therapeutic approach for pediatric short stature, treatment with growth hormone (GH) not only favors the child's individual growth, but also demonstrates effectiveness in conditions such as Turner Syndrome (short girls due to partial or complete deletion of the X chromosome)., Noonan Syndrome (short stature, congenital heart disease due to genetic defect), Prader-Willi Syndrome (short stature, insatiable hunger that often leads to obesity due to changes in chromosome 15 SAVENDAHL, L. et al., 2021).

The titration of medication for the treatment of growth varies between doctors, considering the assessment of the child's speed and amount of growth over time, factors that can be modulated in each patient (MAGHNIE, M. et al., 2022).

Savendahl et al. (2021) highlight that the adverse effects observed in children with growth impairment were significantly low, with the absence of side effects during 5 years of investigation.

Interventional and observational studies conducted over 3 years revealed significant improvements in aspects such as identity recognition and proactivity in children treated with GH. The psychological state is assessed in relation to the final height reached by the child, when compared to a typical adult (MAMELI et al., 2023). These findings indicate not only physical benefits, but also positive impacts on the psychosocial development of treated children. The therapeutic approach with GH, in addition to providing height gains, emerges as a safe and well-tolerated intervention, contributing to psychosocial improvements, which highlights its relevance in the comprehensive management of pediatric short stature.

For children born small for gestational age, who are at high risk of short stature

in adulthood, the search for the etiology of short stature is crucial before starting any therapeutic intervention (CARDOSO-DEMARTINI et al., 2019).

Treatment with growth hormone is considered safe and preferably indicated after 2-4 years of age, aiming to increase growth speed to reach a normal height during childhood and an adult height within the established goal. The response to treatment is variable, being more effective before puberty (CARDOSO-DEMARTINI et al., 2019).

Research indicates that a 52-week treatment with PEG-rhGH growth hormone at doses of 0.1 or 0.2 mg/kg/week resulted in significant improvements in height Z-score and other growth-related variables. Both doses were well tolerated, with similar safety profiles (WIT and JOUSTRA, 2023).

The rhGH therapy demonstrates efficacy in improving height in patients with heterozygous variants in the natriuretic peptide type B receptor gene; semmutated causes short stature. However, the effectiveness of treatment in patients with these variants still requires investigation in a larger sample, with long-term follow-up (CHEN et al., 2023).

Treatment with recombinant human IGF-I is indicated in specific cases, such as Laron syndrome and mutations in growth hormone activation pathways and their membrane receptors, and presents benefits both in height and facial characteristics of these patients (MASTROMAURO, GIANNINI, CHIARELLI, 2023).

In summary, it points to the need for an individualized therapeutic approach for short stature. Early initiation of treatment emerges as a determining factor for its effectiveness, and it is crucial that families are aware of this aspect when making decisions.

FINAL CONSIDERATIONS

The comprehensive analysis of hormonally-related short stature in pediatrics highlights diagnostic complexity, highlighting the need for an individualized clinical approach. Notable advances in assessment methods, including detailed history taking and physical examination, have contributed to the diagnosis of growth hormone deficiency, although challenges remain in interpreting genetic tests and selecting conclusive criteria. Growth hormone treatment has shown efficacy in promoting growth and psychosocial improvements, being relevant in the management of pediatric short stature. However, issues such as medication titration and identifying ideal patients for intervention remain under discussion. The research points to the need for further investigation, including the effectiveness of new treatment modalities and the response in specific cases, such as genetic variants.

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