Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/29/20240827

Early diagnosis and treatment strategies for pediatric growth hormone deficiency

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Abstract. Over the last century, adult height has shown a marked increase, largely attributed to advancements in nutrition and healthcare. Monitoring child growth is crucial for the early identification of growth-related disorders. One such condition is the underperformance of the pituitary gland, which can lead to a deficiency in growth hormone, manifesting as short stature. Therapeutic interventions, such as growth hormone therapy and low-dose androgen therapy, have proven effective. These treatments utilize synthetic hormones to foster normal growth. Prompt and accurate diagnosis, coupled with precise treatment, is critical to empower individuals to reach their maximum growth potential and alleviate associated health concerns. Future research should aim to deepen our understanding of the interplay between pituitary cells, uncover additional genetic factors contributing to short stature, and enhance growth hormone replacement therapies. Such progress will significantly bolster the diagnostic and therapeutic strategies for children with growth impairments.

Keywords: short stature, pituitary gland, growth hormone, androgen

1. Introduction

Short stature, a condition characterized by a height significantly below the average for age and sex, can have profound implications for both physical and psychosocial health. It is often an early indicator of underlying disorders, including growth hormone deficiencies, genetic conditions, or endocrine disruptions. The increasing awareness and understanding of short stature's multifaceted nature have led to an emphasis on the necessity of early diagnosis and treatment. Early therapeutic intervention is crucial as it not only improves growth outcomes but also aids in the amelioration of potential long-term sequelae associated with the condition. This manuscript reviews the pathophysiology, diagnosis, and treatment options for growth hormone-related short stature, underscoring the critical importance of prompt and appropriate intervention.

2. Background Sections

Height serves as a critical marker of a child's overall health and developmental progress, garnering considerable attention from parents and healthcare providers alike. Epidemiological studies have established a correlation between taller adult stature and both increased longevity and a lower incidence of certain health conditions [1-4]. A comprehensive analysis of global data spanning a hundred years, from 1896 to 1996, reveals a notable increase in adult heights across over 200 countries, with the most

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significant gains observed in developed regions such as Europe and North America [5]. This upward trend is also mirrored in countries like Japan, South Korea, Iran, and China, which have witnessed remarkable height increments, exceeding 10 cm, concurrent with their rapid development over the past century. Contrastingly, regions facing developmental challenges, including South Asia and parts of Africa, have experienced only minimal height increases, underscoring the detrimental effects of childhood malnutrition and disease on growth, leading to shorter adult stature. These disparities underscore the need for vigilant monitoring of children's height as part of their growth and development evaluations.

Central to the regulation of growth is the pituitary gland, located at the brain's base [6]. This gland is instrumental in controlling hormone secretion within the body, notably regulating growth hormone synthesis and release via growth hormone-releasing hormone and somatostatin. Disruptions caused by congenital anomalies, neoplasms, or infections can compromise the pituitary gland's function, curtailing normal growth hormone secretion and potentially leading to the onset of short stature. Consequently, ensuring the proper functioning of the pituitary gland is imperative for the normal growth and development of children.

2.1. The Cause of Short Stature

"Short stature" is a term used to describe a condition where an individual's height significantly deviates below the average for their age and sex. The accepted definition of short stature is a height that is more than two standard deviations (SD) below the mean for a given population, a benchmark upheld in clinical settings as well [7-10]. However, it's imperative to understand that short stature is an anomaly only in a statistical context and is not inherently indicative of disease. In a normally distributed population, roughly 2.3% can be expected to fall below this two SD threshold. Diagnoses of short stature may reflect either this statistical variation or a growth-limiting pathological condition.

Height is governed by an interplay of genetic and environmental factors. Short stature arises from a variety of sources, including familial short stature and constitutional growth delay [11-12]. Pathological short stature, often requiring intervention, stems from underlying diseases. In some instances, short stature may be deemed idiopathic when no specific cause is identified. This diagnosis is reserved for otherwise healthy children whose short stature lacks an identifiable etiology [9].

Familial short stature is identified in individuals genetically predisposed to shorter height without any pathological cause [8]. This genetic predisposition manifests as a familial pattern of height distribution. A child's height is likely to mirror the shorter stature of their parents or familial lineage, generally aligning with family-specific height ranges and exhibiting normal growth rates and bone maturation [9].

Constitutional growth delay, a prevalent short stature etiology, is distinguished by a decelerated growth velocity in childhood, leading to a lag in bone maturation and pubertal onset, albeit with eventual attainment of normal adult stature relative to family height norms [12]. Nutritional deficits are postulated to contribute to this delay [11].

Endocrine pathologies, such as growth hormone deficiency, are frequent culprits of pathological short stature [13-15]. Inadequate growth hormone production by the pituitary gland can profoundly impede growth, culminating in short stature.

Genetic syndromes, including but not limited to 3M syndrome, Noonan syndrome, and others, along with mutations in the short stature homeobox gene, are significant contributors to growth impairment [16-17]. These conditions often coincide with hormonal irregularities, compounding the growth challenges.

Chronic conditions like cystic fibrosis and inflammatory diseases may also impinge on growth due to their systemic effects on nutrient uptake and inflammation [11].

Bone dysplasias, including achondroplasia and others, inherently affect bone development, leading to short stature in comparison with the general population [18].

Moreover, precocious puberty, malnutrition, and psychosocial stress are additional factors that can truncate growth, each capable of preventing individuals from realizing their full growth potential [19].

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2.2. Function of the Pituitary Gland

The pituitary gland, also known as the hypophysis, is a central organ in the endocrine system, situated at the brain's base and connected to the hypothalamus via the hypophyseal stalk [20-21]. This gland is comprised of three lobes: the adenohypophysis (anterior lobe), the intermediate lobe, and the neurohypophysis (posterior lobe). The anterior pituitary is recognized as a true endocrine gland, whereas the posterior pituitary is an extension of the hypothalamic neural tissue. The hypothalamus controls the pituitary's hormonal secretions, which are pivotal for neural-endocrine interaction and homeostasis. Often termed the "master gland," the pituitary's hormones stimulate other endocrine glands to secrete a spectrum of hormones, thus playing a vital role in the regulation of bodily functions and maintaining physiological balance.

Nine hormones are secreted by the pituitary gland: one from the intermediate lobe, two from the posterior lobe, and six from the anterior lobe [20-21]. The intermediate lobe releases α-melanocyte-stimulating hormone, which regulates skin pigmentation. The posterior lobe produces oxytocin and vasopressin. Oxytocin is instrumental in triggering uterine contractions during childbirth and lactation, while vasopressin, also known as antidiuretic hormone, is involved in water retention in the kidneys and in elevating blood pressure. Notably, oxytocin and vasopressin are synthesized by the hypothalamus and then stored and released by the posterior lobe, making them hypothalamic or neurosecretory hormones. Additionally, the posterior lobe releases neurophysins, which serve as carrier proteins for oxytocin and vasopressin.

The anterior lobe generates six hormones: growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). GH, the anterior pituitary's most abundant hormone, is critical for the growth and function of muscles, bones, and the heart. It stimulates the liver to release somatomedin (IGF-1) and directly enhances muscle mass. ACTH prompts the adrenal gland to produce glucocorticoids. TSH manages the thyroid gland's release of thyroxine and triiodothyronine. Prolactin is vital for lactation and also participates in osmoregulation, carbohydrate metabolism, and reproduction. FSH is crucial for reproductive processes, stimulating spermatogenesis in males and follicular growth and estradiol secretion in females. LH is essential in the female reproductive system for promoting ovulation, corpus luteum formation, and progesterone secretion. In males, it spurs the Leydig cells to produce testosterone.

2.3. Growth Hormone Related Short Stature

Growth hormone (GH) secretion from the pituitary gland is a critical element in the diagnosis of short stature. Although the role of GH is well-established, the involvement of other pituitary hormones in short stature remains to be elucidated through further research.

GH is essential for normal human growth. The hypothalamus produces growth hormone-releasing hormone (GHRH) and somatostatin, which respectively stimulate and inhibit GH release from the anterior lobe of the pituitary gland. Once secreted, GH acts on various tissues, particularly promoting the secretion of insulin-like growth factor-1 (IGF-1), which is instrumental in bone growth [22].

Pituitary gland dysfunction, due to disease or injury, can reduce or halt GH secretion, causing growth hormone deficiency (GHD). This deficiency severely impacts growth and development in children and adults alike, with children experiencing a notably decreased growth velocity and an inability to achieve expected adult height [23].

GHD can result from congenital abnormalities in the pituitary or hypothalamus, genetic mutations affecting genes such as POU1F1, LHX3, HESX1, OTX2, TBX19, SOX3, and GLI2, which have been linked to GHD [24]. Acquired causes of GHD may include tumors, head trauma, infections, certain medications like methylphenidate, and surgical interventions [25-26]. Correctly identifying the cause of GHD is crucial for appropriate treatment and management.

Bioinactive GH can also lead to short stature, as seen in Laron syndrome. Patients with this syndrome exhibit normal or elevated GH levels but have low serum IGF-1 due to mutations in the growth hormone receptor gene, rendering GH ineffective and necessitating biosynthetic IGF-1 treatment [24].

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2.4. Growth Hormone Therapy

The cornerstone of GHD treatment is the administration of synthetic GH. The therapy's dosage and duration are tailored to the child's growth pattern and height progress [14]. In 1985, the FDA approved recombinant human GH for children with growth failure due to insufficient endogenous GH secretion [14]. The indication was extended in 2003 to include idiopathic short stature, characterized by a height ≤ 2.25 SD below the mean and a projected adult height below the normal range. In 2005, the FDA approved IGF-I for long-term treatment in children with severe IGF-I deficiency or those who develop antibodies to GH, noting that IGF-I is not a replacement for GH therapy and should not be used for secondary deficiencies caused by GHD or malnutrition [14].

Prompt diagnosis and intervention can enable individuals with short stature to attain their expected growth potential and mitigate related symptoms. GH therapy has been validated to enhance growth rates and final adult height in children [13,23,27]. While GH therapy is generally safe, it requires daily injections and can be costly, necessitating careful consideration of the child's specific circumstances, including age, growth rate, bone age, among other factors. Future adverse effects related to GH therapy also warrant consideration in treatment decisions for children with short stature.

2.5. Low Dose Androgen Therapy

Alternative therapies to human growth hormone for promoting growth include low dose androgen therapy with testosterone injections and oral oxandrolone, though they are not FDA-approved for accelerating growth. Controlled trials have indicated that these therapies can enhance annual height growth rates by 3.0 to 5.1 cm over one to three years [28-29]. Comparatively, the costs of androgen treatments are lower than those for growth hormone therapy. In prepubescent children with a bone age under 11 years, oxandrolone is favored to mitigate the risk of premature estrogen-mediated epiphyseal maturation associated with testosterone. Treatment with oxandrolone is discontinued upon detecting increases in endogenous testosterone to minimize side effects. Long-term studies suggest that oxandrolone treatment enables patients to reach or slightly exceed their predicted adult height [30]. The risk of adverse effects, such as hepatic or lipid disturbances, is considered low with low dose androgen therapy, as supported by extensive clinical data [31,28,29].

Aromatase inhibitors have been explored to extend pubertal growth and height in boys, but they are costlier and less effective in accelerating growth than androgen therapy. Post-treatment heights with aromatase inhibitors have been shorter than predicted by 4.1 to 6.1 cm. Additionally, the potential risks of estrogen deficiency during puberty, such as vertebral deformities, limit the recommendation of aromatase inhibitors for short stature outside of experimental studies.

3. Research Frontier and Prospects

3.1. Study of Interactions Among Pituitary Cells

While previous research has focused on the relationship between pituitary cells and growth hormone, emerging studies highlight the significance of interactions among pituitary cells in growth and development [32-33]. Future research should explore the signaling and regulatory mechanisms within pituitary cell populations to understand their impact on growth hormone secretion and the development of short stature. Advanced methodologies, including functional studies and gene editing, are recommended for a comprehensive understanding of these intraglandular processes.

3.2. Association between Genetic Inheritance and Short Stature

Several gene mutations have been implicated in short stature [24], but the genetic underpinnings of the condition require further exploration. Upcoming studies should aim to identify genetic mutations linked to short stature and examine their effects on the pituitary gland's functionality and growth hormone signaling. The advent of sophisticated genetic sequencing technologies holds the promise of uncovering additional mutations and elucidating their influence on growth processes.

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3.3. Development of More Effective Growth Hormone Replacement Therapy

While growth hormone therapy has been beneficial, its variable efficacy and potential side effects call for improvement. Research should be directed towards devising more effective and safer growth hormone replacement therapies to elevate treatment outcomes and life quality for those with short stature. Advances in gene editing and therapy are expanding the horizon for genetic interventions in short stature treatment. Identifying new gene mutations and investigating gene correction methods to restore normal growth hormone activity and bone development are crucial future research avenues.

4. Conclusion

The evaluation and management of short stature is a complex yet critical endeavor in pediatric healthcare, with implications that extend into adulthood. This review has elucidated the multifaceted nature of short stature, emphasizing the pivotal role of the pituitary gland in growth regulation, the diverse etiologies underlying the condition, and the importance of early and accurate diagnosis for effective intervention. Growth hormone therapy, as the mainstay treatment, and low dose androgen therapy, as a cost-effective alternative, have shown promise in addressing growth hormone deficiencies, although their use must be carefully tailored to individual patient needs and circumstances.

Early intervention in cases of short stature is not merely a matter of improving physical growth parameters but is also about enhancing overall health outcomes, psychosocial well-being, and quality of life. The prospects of achieving normal adult height and mitigating the risks associated with short stature hinge on timely diagnosis, which in turn relies on a keen understanding of the condition's genetic, hormonal, and environmental factors.

Future research, particularly in the realms of pituitary cell interactions, genetic inheritance, and the development of more effective growth hormone therapies, holds the potential to revolutionize the treatment landscape for short stature. The advancement of gene editing and therapy techniques offers a beacon of hope for targeted and curative treatments that could address the root causes of growth impairments.

Ultimately, the collective goal of healthcare providers, researchers, and families is to ensure that children with growth hormone-related short stature receive the most effective care from the earliest point possible, setting a trajectory for healthier and fuller lives.

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