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Relationship Between Growth Hormone Deficiency and Neurodevelopmental Disorders in Children

Ronaldo Freua Bufaíçal Filho[1], Carlos Henrique Marchiori[1]*, Klebert De Paula Malheiros[1]
[1]Ronaldo Bufaíçal Institute

Abstract: Growth Hormone (GH) is essential for human development, not only by regulating postnatal growth and metabolism but also by supporting key neurodevelopmental processes. Its biological actions extend to neurogenesis, synaptogenesis, myelination, and the modulation of brain networks involved in cognition and behavior. Evidence from neuroimaging indicates that children with Growth Hormone Deficiency (GHD) often present reduced hippocampal volume, alterations in white matter integrity, and disrupted connectivity, findings that correlate with deficits in learning, attention, and executive functioning. These observations demonstrate that GHD should not be viewed exclusively as a disorder of stature but also as a condition with potential neurocognitive consequences. Clinical studies show that GHD manifests with proportionate short stature, delayed puberty, and metabolic alterations, but also with difficulties in memory, learning, and behavior. This article aims to review the physiological mechanisms, clinical manifestations, diagnostic approaches, therapeutic advances, and future perspectives of GH, with a special emphasis on recent developments. By integrating knowledge across two and a half decades, the text provides a robust and updated overview of the growth hormone field. This study was conducted as an integrative literature review focused on the relationship between GHD and neurodevelopmental disorders in children. The review aimed to synthesize current knowledge on physiological mechanisms, clinical manifestations, syndromic associations, therapeutic approaches, and neurocognitive outcomes. A structured search was carried out in major databases, including PubMed, Scopus, Web of Science, and Google Scholar, between January 2000 and August 2025. The keywords and their combinations were used: growth hormone deficiency, children, neurodevelopment, cognition, Prader-Willi syndrome, Turner syndrome, attention deficit hyperactivity disorder (ADHD), autism, recombinant human growth hormone, and long-acting growth hormone. Syndromic conditions such as Prader–Willi and Turner syndromes.

Keywords: Autism, Children, Cognition, Syndromic, Therapeutic.

Research Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Ronaldo Bufaíçal Institute

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INTRODUCTION

1.1. General concepts of growth hormone and neurodevelopment

Growth hormone (GH), also known as somatotropin, is a peptide hormone secreted by somatotroph cells in the anterior pituitary gland. It is widely recognized for its role in promoting postnatal linear growth, but its actions extend far beyond skeletal development. GH influences protein synthesis, lipid metabolism, glucose regulation, cardiovascular health, and neurodevelopmental processes (Figure 1) (Murray *et al.*, 2016; Collett-Solberg *et al.*, 2019).

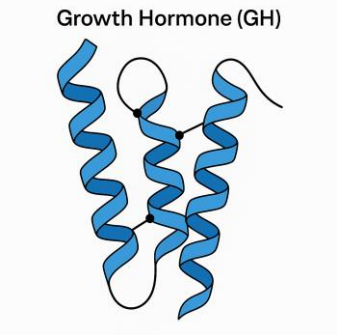

Figure 1: Chemical structure of Growth Hormone (GH). Ribbon diagram representation of the GH protein showing its alpha-helices and disulfide bonds, compacted to fit clearly

Structurally, GH is a single-chain polypeptide of about 191 amino acids stabilized by disulfide bonds. Its biological effects are mediated through the Growth Hormone Receptor (GHR) and the Growth Hormone Binding Protein (GHBP). Upon binding to its receptor, GH triggers dimerization and activation of intracellular cascades involving Janus kinase 2 (JAK2), Signal Transducers and Activators of Transcription (STAT), and Mitogen-Activated Protein Kinase (MAPK). These pathways ultimately regulate the transcription of genes responsible for somatic growth and the production of Insulin-Like Growth Factor 1 (IGF-1), a crucial mediator of GH's effects on the body and brain (Collett-Solberg *et al.*, 2019; Coutant *et al.*, 2023).

The developing brain needs a complex interaction of genetic, environmental, and hormonal factors. GH and IGF-1 receptors are located in the hippocampus, cerebral cortex, and cerebellum, brain regions vital for learning, memory, emotional regulation, and motor skills. Experimental studies show that GH encourages neurogenesis, synaptogenesis, dendritic branching, and myelination, all essential for healthy neural circuit development (Devesa *et al.*, 2016; Tang *et al.*, 2022). Clinical and neuroimaging findings support this biological evidence. Children with GHD often show reduced hippocampal volume, alterations in white matter integrity, and disruption of large-scale brain networks, which may explain difficulties in cognition, attention, memory, and executive functioning (Figure 2) (Tang *et al.*, 2022; Cheng *et al.*, 2024).

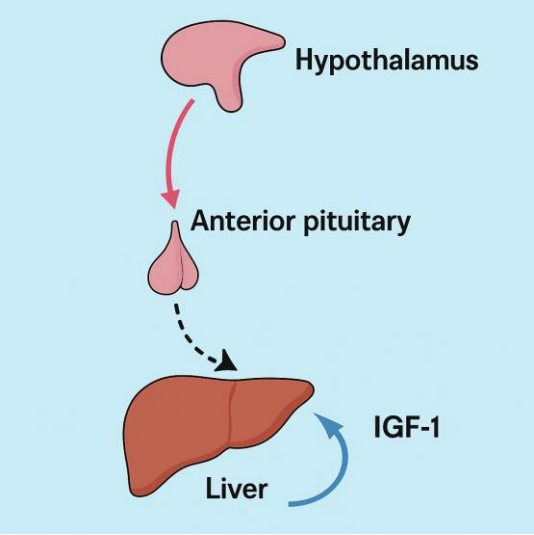

Figure 2: Physiological pathways of GH and IGF-1. Diagram showing the hypothalamus–pituitary–GH axis, activation of the JAK2/STAT5 pathway, IGF-1 production in the liver, and effects on bone, muscle, and brain

Another key connection between GH and neurodevelopment is sleep. GH secretion peaks during slow-wave sleep, and disturbances in this rhythm are linked to learning difficulties and behavioral dysregulation. The GH–sleep relationship is bidirectional: impaired secretion affects neurodevelopment, and neurodevelopmental disorders themselves may disrupt GH release (Table 1) (Zaffanello *et al.*, 2024; Bucis, 2025).

Table 1: Hormone growth exerts multiple effects on neurodevelopment, beyond its role in promoting somatic growth. GH and its mediator, insulin-like growth factor 1 (IGF-1), regulate neurogenesis, myelination, synaptic plasticity, and neurotransmitter regulation

Neurodevelopmental Process	Role of Growth Hormone (GH)
Neurogenesis	Stimulates the proliferation of neural progenitor cells and hippocampal growth.
Myelination	Promotes oligodendrocyte activity and axonal myelination, supporting neural conduction.
Synaptic plasticity	Enhances synapse formation and long-term potentiation, essential for learning and memory.
Cortical connectivity	Supports structural and functional connectivity across brain regions.
Cognition and behavior	Improves attention, memory, visuospatial skills, and adaptive functioning.
Sleep regulation	Strongly linked to slow-wave sleep, promoting brain restorative processes.

Overall, GH is not simply a growth regulator but a multisystem hormone with profound effects on brain maturation. Its deficiency in childhood is therefore not only a disorder of stature but also a condition with potential long-term consequences for cognition, learning ability, and risk of neurodevelopmental disorders (Table 2) (Perenc *et al.*, 2019; Vahdatpour *et al.*, 2016).

Table 2: While GHD in children primarily leads to impaired growth and delayed neurocognitive outcomes, GH excess in adults (acromegaly) causes tissue overgrowth, metabolic complications, and in some cases, cognitive alterations

Domain	GH Deficiency (GHD)	GH Excess (Acromegaly)
Growth/Body Composition	Short stature, increased fat mass (especially visceral), and reduced lean body mass.	Excessive growth (before epiphyseal closure), acral enlargement, increased muscle mass, but abnormal proportions.
Metabolism	Improved insulin sensitivity (untreated children), dyslipidemia, and visceral adiposity.	Insulin resistance, hyperglycemia, diabetes, dyslipidemia.
Neurocognitive Impact	Attention deficits, slower processing speed, reduced visuospatial ability, fatigue, and mood changes.	Headaches, sleep apnea, fatigue, cognitive complaints, and mood disturbances.
Skeletal System	Osteopenia, characterized by a risk of fractures due to low bone turnover.	Arthropathy, vertebral deformities, increased bone turnover, but abnormal architecture.
Cardiovascular Risk	Atherosclerosis, endothelial dysfunction, and increased intima-media thickness.	Hypertension, cardiomyopathy, and increased cardiovascular morbidity.
Sleep and Regulation	Reduced GH linked to poor slow-wave sleep, altered circadian rhythm.	Sleep-disordered breathing (obstructive sleep apnea), fatigue.

Taken together, evidence accumulated from 2000 to 2025 highlights GH as not merely a growth-promoting peptide, but rather a multifunctional regulator of human biology.

1.2. Clinical manifestations and neurodevelopmental syndromes

GHD in childhood is a rare disorder, with an estimated prevalence of one in 4,000 children worldwide. Clinically, it is characterized by proportionate short stature, delayed bone age, neonatal hypoglycemia, slow growth velocity, and delayed puberty. While the physical phenotype is often the first sign leading to diagnosis, neurocognitive and behavioral difficulties are increasingly recognized as part of the clinical spectrum (Table 3) (Chinoy & Murray, 2016; Murray *et al.*, 2016).

Table 3: Children with GHD often present with proportionate short stature, delayed bone age, increased fat mass, reduced muscle strength, and, in some cases, hypoglycemia

Manifestation	Description
Short stature	Proportionate reduction in height for age.
Delayed bone age	Skeletal maturation behind chronological age.
Neonatal hypoglycemia	Low blood sugar in the newborn period.
Slow growth velocity	Reduced height progression.
Pubertal delay	Late onset of secondary sexual characteristics.
Cognitive deficits	Impaired memory, learning, and attention.

Children with GHD frequently exhibit learning difficulties, reduced attention span, impaired working memory, and delayed psychomotor development. Such features are supported by neuroimaging studies, which demonstrate structural brain alterations in the hippocampus and frontal lobes that correlate with

cognitive deficits. Importantly, these difficulties may persist even when stature is treated with recombinant GH, underscoring the need for a comprehensive neurodevelopmental approach (Tang *et al.,* 2022; Cheng *et al.,* 2024).

In summary, the clinical manifestations of GHD evolve across the lifespan, from neonatal hypoglycemia and poor growth in children to metabolic dysfunction in adults. Diagnosis requires a multifaceted approach, combining auxological data, biochemical markers, stimulation tests, and neuroimaging, while always considering alternative diagnoses. Advances since 2000 have refined testing protocols, updated stimulation cutoffs, and improved diagnostic accuracy, ensuring that therapy is targeted to those most likely to benefit. As a result, early recognition and precise diagnosis remain critical to optimizing outcomes for patients with GHD (Tang *et al.,* 2022; Cheng *et al.,* 2024).

1.3. Growth hormone and metabolism

Growth hormone (GH) is not only essential for linear growth but also a critical regulator of human metabolism, influencing carbohydrate, lipid, and protein homeostasis. Its effects are both direct, via signaling in peripheral tissues, and indirect, mediated by insulin-like growth factor-1 (IGF-1). In carbohydrate metabolism, GH reduces glucose uptake in skeletal muscle and adipose tissue while stimulating hepatic gluconeogenesis, which contributes to relative insulin resistance. Children with GH deficiency (GHD) often display enhanced insulin sensitivity, and replacement therapy restores metabolic balance (Chinoy and Murray, 2016; Murray *et al.,* 2016; Collett-Solberg *et al.,* 2019).

Conversely, excess GH, as in acromegaly, is strongly linked to impaired glucose tolerance and diabetes. More recently, Tavares *et al.* (2024) demonstrated that GH action on hypothalamic Sim1 and VGLUT2 neurons directly modulates insulin sensitivity and hepatic glucose output, redefining its role as both a peripheral and central metabolic regulator. Regarding lipid metabolism, GH promotes lipolysis, thereby increasing the mobilization of free fatty acids for energy. GHD leads to visceral adiposity, while GH replacement reduces fat mass and improves body composition. GH also enhances protein metabolism through IGF-1–mediated pathways, supporting muscle anabolism and strength (Ben-Shlomo and Melmed, 2006; Devesa *et al.,* 2016; Grugni *et al.,* 2023).

The interaction of GH with other hormones further regulates metabolism. Adequate insulin is required for IGF-1 synthesis, thyroid hormones synergize with GH in energy expenditure, and sex steroids amplify its metabolic effects, while glucocorticoids blunt GH action. Obesity and poor sleep significantly reduce GH secretion, leading to a state described as functional GH deficiency. Clinically, untreated GHD in adults is associated with dyslipidemia, visceral fat accumulation, and higher cardiovascular risk. Replacement therapy improves lipid profiles and vascular health when IGF-1 is kept within the normal range (Vahdatpour *et al.,* 2016; Woelfle *et al.,* 2024; Zaffanello *et al.,* 2024).

In summary, GH integrates hypothalamic, pituitary, and peripheral signals to regulate glucose, lipid, and protein metabolism. Discoveries over the last two decades, particularly its central role in hypothalamic circuits, underscore GH as a systemic regulator of energy balance, with major implications for both deficiency and replacement therapies.

1.4. Small for Gestational Age (SGA) and familial short stature

Children born small for gestational age (SGA) who fail to achieve catch-up growth may be eligible for GH therapy. International consensus guidelines emphasize careful evaluation of etiology, growth trajectories, and long-term risks such as metabolic syndrome and learning difficulties (Hokken-Koelega *et al.,* 2023).

Similarly, familial short stature and constitutional growth delay, although typically benign, must be differentiated from pathological GHD to ensure appropriate management (Aguilar and Castano, 2023).

1.5. Neurodevelopmental disorders: ADHD and autism

The relationship between GHD and neurodevelopmental disorders such as ADHD and autism spectrum disorder (ASD) is complex. Children with ADHD have been reported to show higher rates of impaired GH stimulation responses, suggesting possible alterations in GH–IGF-1 axis regulation (Figure 3) (Perenc *et al.,* 2019).

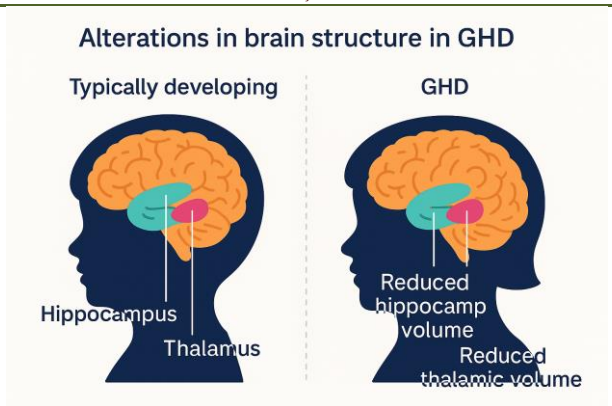

Figure 3: Alterations in brain structure in GHD. Diagram comparing brain structures in typically developing children and those with GHD, focusing on reduced hippocampal and thalamic volumes.
Source: Cheng *et al.,* 2024

In ASD, IGF-1 and related compounds have been investigated for their neurotrophic potential, with some evidence supporting benefits on synaptic function and behavioral outcomes, although results remain inconclusive. These findings highlight potential shared biological pathways, but causality remains unproven and requires further longitudinal research (Vahdatpour *et al.,* 2016).

1.6. Treatment approaches and recent advances

The standard treatment for growth hormone deficiency (GHD) in children is recombinant human growth hormone (rhGH), administered through daily subcutaneous injections. RhGH therapy has consistently demonstrated efficacy in normalizing growth velocity, increasing final adult height, improving body composition, and reducing fat mass (Table 4) (Collett-Solberg *et al.,* 2019; Woelfle *et al.,* 2024).

Table 4: Recombinant human GH (rhGH) therapy remains the standard of care. Traditionally, daily subcutaneous injections have been used, but long-acting formulations have recently been introduced. The study compares the two strategies in terms of efficacy, adherence, and safety

Treatment Type	Advantages	Limitations
Daily rhGH	Established efficacy; long-term safety; widely available.	Requires daily injections; adherence issues.
Long-acting GH (LAGH)	Reduced injection frequency; potential for better adherence.	Limited long-term data; molecule-specific pharmacology.
Aspect	Daily rhGH.	Long-acting GH (LAGH).
Administration	Daily subcutaneous injections.	Weekly or less frequent subcutaneous injections.
Treatment duration	Standard of care for over 40 years.	Recently introduced, under evaluation in real-world settings.
Efficacy	Proven efficacy in growth, body composition, and metabolic outcomes	Comparable efficacy in clinical trials, still under long-term evaluation.
Adherence	Challenging due to daily administration, risk of poor compliance.	Improved adherence is expected due to reduced injection frequency.
Safety	Well-established safety profile, common mild side effects (edema, joint pain)	Similar safety profile to daily GH, but long-term data are limited.
Indications	Children and adults with GHD, Turner syndrome, Prader–Willi syndrome, SGA, and chronic renal failure.	Approved for GHD in children and adults, some molecules are not yet widely available.
Accessibility	Widely available in most healthcare systems, often included in public protocols.	Limited access in many countries, not always covered by public health or insurance.

Beyond its somatic benefits, several longitudinal studies report improvements in neurocognitive domains such as working memory, processing speed, and attention, particularly when therapy is initiated early in life and maintained with good adherence (Figure 4) (Tanaka *et al.,* 2019).

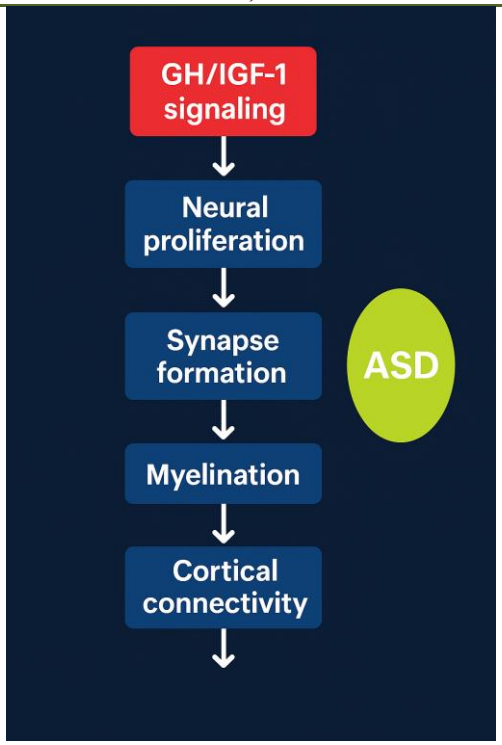

Figure 4: Shared GH/IGF-1 and ASD. Flowchart showing how GH/IGF-1 signaling influences neural proliferation, synapse formation, myelination, and cortical connectivity, with links to autism spectrum disorder
Source: Tang *et al.*, 2022, and Vahdatpour *et al.*, 2016

1.7. Recombinant DNA technology

The introduction of rhGH in the 1980s, produced via Recombinant DNA (rDNA) technology, replaced earlier unsafe preparations derived from human pituitary tissue. rDNA technology enabled large-scale, pure, and safe production of GH, eliminating the risk of prion-related diseases such as Creutzfeldt–Jakob, which had previously occurred in some patients treated with cadaveric GH (Science, 2025). This innovation not only transformed treatment availability but also ensured the standardization of GH therapy worldwide.

1.8. Long-Acting Growth Hormone (LAGH)

A major advance in recent years has been the development of Long-Acting Growth Hormone (LAGH) formulations designed to reduce the burden of daily injections. Weekly preparations, such as somatrogon and somapacitan, have been approved in several countries, while others, like lonapegsomatropin, are available in the United States and Europe, and jintrolong has been marketed in China for over a decade (Martins, 2025).

Clinical studies show that LAGH provides comparable efficacy to daily GH in promoting linear growth in both children and adults, with similar safety profiles. The reduction in injection frequency may enhance treatment adherence, a critical factor in achieving optimal outcomes. However, real-world data confirming improved adherence and long-term neurodevelopmental benefits are still limited (Martins, 2025).

1.9. GH in special clinical contexts

GH has also been studied as an adjuvant therapy in reproductive medicine, particularly for women with poor ovarian response undergoing In Vitro Fertilization (IVF). Some meta-analyses suggest that GH co-treatment may increase oocyte yield, improve embryo quality, and enhance clinical pregnancy rates. However, guidelines from the European Society of Human Reproduction and Embryology (ESHRE) caution that current evidence remains insufficient for routine recommendation (ESHRE Guideline Group, 2020; Lin *et al.*, 2023).

1.10. Risks and non-medical uses

Despite its established medical indications, GH has also been misused in non-therapeutic contexts, particularly for aesthetic purposes and performance enhancement in sports. Although GH can reduce fat mass nd increase lean body mass, such off-label use carries serious health risks, including insulin resistance, fluid retention, carpal tunnel syndrome, acromegaly, and increased risk of neoplasia due to its mitogenic properties. Regulatory authorities, such as the Brazilian Federal Council of Medicine, prohibit GH prescriptions for aesthetic purposes, reinforcing that its use should remain confined to approved medical indications (Bucis, 2025; Capixaba Reporter, 2025).

1.11. Pulsatile secretion and circadian rhythm

GH is secreted in a pulsatile fashion, with 6–12 peaks per day. The most prominent surge occurs shortly after the onset of slow-wave sleep, reflecting the

integration of sleep architecture and endocrine rhythms. Smaller peaks are triggered by exercise, fasting, hypoglycemia, and stress, whereas feeding, hyperglycemia, and elevated free fatty acids suppress GH release (Van Cauter *et al.,* 2000; Zaffanello *et al.,* 2024).

This pulsatility is crucial: continuous GH exposure downregulates its receptor, whereas intermittent surges maintain sensitivity and allow differential regulation of metabolic and anabolic pathways. Age modifies this pattern significantly: children and adolescents exhibit higher amplitude and frequency of pulses, whereas secretion declines progressively with aging, a phenomenon sometimes referred to as somatopause (Murray *et al.,* 2016; Collett-Solberg *et al.,* 2019).

1.12. Objective

This article aims to review the physiological mechanisms, clinical manifestations, diagnostic approaches, therapeutic advances, and future perspectives of GH.

2.0. METHODS

A study was conducted as an integrative literature review focused on the relationship between GHD and neurodevelopmental disorders in children. The review aimed to synthesize current knowledge on physiological mechanisms, clinical manifestations, syndromic associations, therapeutic approaches, and neurocognitive outcomes. A structured search was carried out in major databases, including PubMed, Scopus, Web of Science, and Google Scholar, between January 2000 and August 2025. The following keywords and their combinations were used: growth hormone deficiency, children, neurodevelopment, cognition, Prader-Willi syndrome, Turner syndrome, ADHD, autism, recombinant human growth hormone, and long-acting growth hormone. The inclusion criteria were:1. Articles published in English between 2000 and 2025. This approach enabled an integrated synthesis of current evidence, highlighting both consolidated knowledge and persistent research gaps.

3.0. STUDY SELECTION

3.1. Cognitive and behavioral implications

The relationship between GHD and neurodevelopmental outcomes has become increasingly evident through clinical, experimental, and neuroimaging studies. While GHD has traditionally been approached as a disorder of stature, current evidence highlights that its impact is multisystemic, extending to cognition, behavior, sleep, and long-term psychosocial adaptation. Children with untreated GHD frequently present learning difficulties, attentional deficits, and executive dysfunction. Neuroimaging findings of disrupted hippocampal and frontal connectivity provide structural correlates for these clinical features. Importantly, while rhGH therapy improves growth outcomes and may partially enhance cognitive performance, responses are heterogeneous. Factors such as age at treatment initiation, treatment duration, genetic background, and comorbidities influence neurodevelopmental outcomes (Table 5) (Tanaka *et al.,* 2019; Tang *et al.,* 2022; Cheng *et al.,* 2024).

Table 5: Several longitudinal studies have reported improvements in memory, attention, and executive functions following GH replacement therapy. Table 5 summarizes evidence from 2000 to 2025 regarding neurocognitive responses to treatment

Outcome Domain	Without Treatment	With GH Treatment
Working memory	Reduced capacity.	Improvement reported in longitudinal studies.
Attention	Frequent deficits, ADHD-like symptoms.	Improved control in some patients.
Learning ability	Lower academic performance.	Better progress with early therapy.
Behavioral regulation	Emotional instability, executive dysfunction.	Partial improvement, heterogeneous response.

3.2. Syndromic and neurodevelopmental disorders

The role of growth hormone (GH) in neurodevelopment has become increasingly evident in the past two decades. Beyond its well-established effects on linear growth and metabolism, GH exerts direct actions within the central nervous system (CNS) through its receptor, which is expressed in several brain regions, including the hippocampus, hypothalamus, and cerebral cortex. These findings suggest that GH participates in neuronal proliferation, myelination, synaptic plasticity, and cognitive processes, establishing it as an important neurotrophic factor (Vahdatpour *et al.,* 2016; Perenc *et al.,* 2019; Grugni *et al.,* 2023; Hokken-Koelega *et al.,* 2023; Aversa *et al.,* 2024).

Clinical studies have shown that children with growth hormone deficiency (GHD) may exhibit more than just short stature. Cognitive and behavioral differences, such as reduced attention span, slower processing speed, and impaired visuospatial skills, have been reported in both untreated and late-diagnosed patients. These manifestations are not universal but appear in a significant subset, highlighting the variability of GH effects on brain function. Importantly, GH replacement has been associated with improvements in certain neurocognitive outcomes, particularly when initiated early in life, which reinforces the importance of timely diagnosis and treatment (Grugni *et al.,* 2023; Aversa *et al.,* 2024).

Neuroimaging research has provided direct evidence of GH-related changes in brain networks. In 2022, Tang and colleagues reported that children with GHD showed disrupted dynamic connectivity across frontal and parietal regions, which are vital for executive function and working memory. In 2024, Cheng et al. demonstrated modifications in morphological similarity networks, especially involving cortico-striatal and cortico-cerebellar pathways. These findings suggest that GHD is linked to structural and functional reorganization of the brain, which may account for some of the cognitive issues observed clinically (Vahdatpour *et al.,* 2016; Grugni *et al.,* 2023; Hokken-Koelega *et al.,* 2023).

Several syndromes illustrate the intersection between GH and neurodevelopment. Prader–Willi syndrome (PWS) is one of the most studied, characterized by hypotonia, hyperphagia, short stature, and intellectual disability. GH therapy in PWS not only improves growth and body composition but has also been linked to better motor function, adaptive behavior, and, in some cases, cognitive development. Close monitoring is required due to comorbidities such as scoliosis and sleep-disordered breathing; however, the overall benefits highlight the dual somatic and neurodevelopmental actions of GH (Perenc *et al.,* 2019; Hokken-Koelega *et al.,* 2023; Aversa *et al.,* 2024).

In Turner syndrome, GH therapy is used primarily to improve adult height, but psychosocial benefits related to self-esteem and social adaptation indirectly support cognitive and emotional development. In children born small for gestational age (SGA) without catch-up growth, GH treatment improves height and has been associated with gains in motor skills and attention, although results are heterogeneous (Table 6) (Perenc *et al.,* 2019; Grugni *et al.,* 2023; Hokken-Koelega *et al.,* 2023).

Table 6: Some genetic syndromes, such as Turner syndrome, Prader–Willi syndrome, and Noonan syndrome, present with GHD or GH insensitivity. The highlights syndromic associations where short stature coincides with significant neurocognitive impairment

Syndrome	Genetic/Clinical Features	GH-related Aspects
Prader–Willi syndrome	Chromosome 15q11–q13 deletion, hyperphagia, obesity, and intellectual disability.	GH therapy improves growth, body composition.
Turner syndrome	Monosomy X, short stature, gonadal dysgenesis, cardiovascular defects.	GH therapy increases final height.
Small for Gestational Age (SGA)	Low birth weight/length, failure of catch-up growth	Eligible for GH if growth failure persists.
Constitutional Growth Delay	Delayed puberty, short familial stature background.	Requires differentiation from pathological GHD.
Idiopathic GHD	Isolated short stature, delayed puberty.	Reduced attention, slower processing speed, partial improvement with GH replacement.
Chronic Kidney Disease-associated Growth Failure	Stunted growth, metabolic disturbances	Neurocognitive delay related to both renal disease and growth deficiency, GH therapy is beneficial.

Experimental evidence complements these clinical observations. Animal models have shown that GH and IGF-1 stimulate hippocampal neurogenesis, reduce apoptosis, and enhance synaptic plasticity. In humans, GH replacement has been associated with improvements in fatigue, mood, and anxiety, suggesting broader effects on brain circuits that extend beyond cognition. Moreover, GH secretion itself is closely tied to sleep regulation, particularly slow-wave sleep, indicating a bidirectional relationship where sleep influences GH release and GH in turn modulates brain restorative processes (Hokken-Koelega *et al.,* 2023; Aversa *et al.,* 2024).

Despite these advances, challenges remain. Not all children with GHD demonstrate measurable cognitive impairment, and the magnitude of neurocognitive benefits from GH therapy varies widely. Factors such as age at diagnosis, underlying etiology, genetic background, and the presence of syndromic conditions influence outcomes. This variability underscores the need for a personalized approach, integrating endocrine treatment with neuropsychological evaluation and educational support (Grugni *et al.,* 2023; Hokken-Koelega *et al.,* 2023; Aversa *et al.,* 2024).

GH is increasingly recognized as a hormone with neurotrophic and cognitive functions. Evidence accumulated from 2000 to 2025 shows that GHD is not solely a growth disorder but also a condition with potential consequences for brain development and function. Early recognition and treatment of GHD may help optimize not only somatic growth but also cognitive performance, adaptive behavior, and quality of life.

3.3. Clinical Relevance

Understanding GH physiology has direct diagnostic and therapeutic implications. Disorders of pulsatile secretion may mimic GHD, while obesity or chronic illness can lower GH secretion without true

pituitary deficiency. Moreover, recognition of regulatory variability has refined cut-off values for stimulation tests, leading to updated guidelines over the past two decades. Finally, recent discoveries (2024–2025) reveal that GH acts within the hypothalamus to regulate insulin sensitivity and glucose production, introducing a new layer of central control that may influence therapeutic strategies for diabetes and metabolic disease (Collett-Solberg *et al.,* 2019; Tavares *et al.,* 2024; Woelfle *et al.,* 2024; Donato, 2025).

3.4. Genetics and etiology of Growth Hormone Deficiency (GHD)

Growth hormone deficiency (GHD) is a heterogeneous disorder that may occur as an isolated condition or as part of combined pituitary hormone deficiencies. Its causes are broadly classified as congenital/genetic or acquired, though overlap in clinical presentation is frequent. Advances in molecular genetics and neuroimaging over the past two decades have reshaped the classification and management of GHD, allowing for more individualized treatment approaches (Collett-Solberg *et al.,* 2019; Woelfle *et al.,* 2024; Donato, 2025).

Among genetic causes, mutations in GH1, the gene encoding pituitary GH, are well established and may impair synthesis or secretion, leading to proportionate short stature, reduced IGF-1 levels, and abnormal GH stimulation responses. GHR mutations cause resistance to GH, known as Laron syndrome, characterized by high GH but low IGF-1. Mutations in STAT5B further emphasize the role of downstream GH signaling, as they impair IGF-1 transcription and are also associated with immune dysregulation (Collett-Solberg *et al.,* 2019; Woelfle *et al.,* 2024; Donato, 2025).

The GH gene cluster on chromosome 17 includes GH1, GH2, and chorionic somatomammotropin genes, highlighting the relevance of GH throughout life, including fetal growth. In addition, transcription factor defects such as POU1F1, PROP1, HESX1, and SOX3 disrupt pituitary development and cause combined deficiencies often associated with midline defects and congenital (Collett-Solberg *et al.,* 2019).

In terms of epidemiology, congenital GHD is estimated to occur in approximately 1 in 4,000 to 1 in 10,000 live births, while acquired forms are more common in oncology survivors and patients with CNS trauma. The distinction between these forms is clinically important because congenital GHD often requires lifelong replacement, whereas acquired GHD may evolve, necessitating repeated evaluations of pituitary function. Moreover, transient or idiopathic GHD, often diagnosed in childhood, may resolve during adolescence or adulthood, underscoring the importance of retesting during transition care (Collett-Solberg *et al.,* 2019; Woelfle *et al.,* 2024; Donato, 2025).

Overall, the genetics and etiology of GHD highlight the complexity of the GH/IGF-1 axis. Over the last two decades, the combination of molecular genetics, improved imaging, and longitudinal clinical studies has shifted the approach from a purely clinical diagnosis to a precision medicine paradigm. This enables clinicians to distinguish between isolated, syndromic, congenital, and acquired causes, improving both prognosis and therapeutic strategies. As our understanding of the genetic architecture expands, the next frontier will be integrating genomics and neuroimaging with personalized GH replacement regimens to optimize growth, metabolic outcomes, and neurocognitive development.

3.5. Molecular mechanisms of GH action

The GH Receptor (GHR) belongs to the cytokine receptor superfamily. Upon ligand binding, two GHR molecules dimerize, activating Janus kinase 2 (JAK2), which phosphorylates tyrosine residues on the receptor and recruits downstream signaling molecules. Key signaling pathways include:

1. **JAK2/STAT5:** The canonical route, leading to transcription of IGF-1, IGFBP-3, and acid-labile subunit (ALS), essential for linear growth and anabolic effects.
2. **MAPK/ERK:** Regulates proliferation and differentiation in bone and cartilage.
3. **PI3K/AKT:** Mediates metabolic effects, including glucose uptake and lipid metabolism (Woelfle *et al.,* 2024; Donato, 2025).

This molecular framework explains why GH affects not only growth plates and muscles, but also adipose tissue, liver metabolism, and even neuronal plasticity. Recent studies highlight tissue-specific variations in signaling, with some pathways predominating in skeletal growth while others dominate in metabolic adaptation (Kim, 2020; Tavares *et al.,* 2024).

3.6. Variability across the lifespan

GH physiology changes across different stages of life:

1. **Infancy:** GH is important for regulating body composition, but growth is more strongly driven by nutrition and insulin.
2. **Childhood:** GH becomes progressively important for linear growth, particularly after age 2.
3. **Puberty:** GH secretion increases dramatically, synergizing with sex steroids to drive the pubertal growth spurt.
4. **Adulthood:** GH maintains metabolic homeostasis, regulating lean body mass, adiposity, and bone turnover.
5. **Aging:** GH secretion declines steadily, contributing to increased adiposity, reduced muscle mass, and decreased bone density (somatopause).

These age-related variations explain why GHD presents differently across the lifespan, from short stature

in children to changes in body composition and quality of life in adults (Chinoy and Murray, 2016; Collett-Solberg *et al.*, 2019).

3.7. Influence of sleep, exercise, and nutrition

1. **Sleep:** GH secretion is tightly coupled with slow-wave sleep. Sleep disorders or sleep deprivation can markedly blunt GH release, with downstream effects on growth and metabolism (Zaffanello *et al.*, 2024).
2. **Exercise:** Acute bouts of exercise, especially resistance and high-intensity training, stimulate GH secretion. Chronic exercise maintains somatotrophic function and may attenuate age-related decline.
3. **Nutrition:** Fasting increases GH release, while obesity suppresses it. Elevated free fatty acids inhibit GH secretion, linking adiposity with impaired somatotrophic signaling. Protein-rich meals (arginine, lysine) can stimulate secretion, a principle that has been used in dynamic testing protocols (Kim, 2020; Tavares *et al.*, 2024)

3.8. Integration with other hormonal axes

The GH/IGF-1 system is deeply interconnected with other hormonal axes:

1. **Thyroid hormones:** Synergize with GH for skeletal growth.
2. **Sex steroids:** Amplify GH secretion during puberty.
3. **Insulin:** Modulates hepatic production of IGF-1; portal insulin deficiency, as in type 1 diabetes, impairs IGF-1 synthesis despite elevated GH.
4. **Cortisol:** Chronic excess, as in Cushing's syndrome, blunts GH secretion and action.

These interconnections underscore GH's role as a systemic integrator of growth, reproduction, and metabolism (Kim, 2020; Tavares *et al.*, 2024).

3.9. Hypothalamic and peripheral regulators

The hypothalamus is the principal driver of GH secretion through two neuropeptides:

1. Growth hormone–releasing hormone (GHRH), produced in the arcuate nucleus, stimulates GH synthesis and release via cAMP and PKA-dependent mechanisms.
2. Somatostatin (SMS), secreted from the periventricular nucleus, exerts tonic inhibitory control by suppressing calcium influx in somatotrophs (Figure 5) (Kim, 2020; Tavares *et al.*, 2024).

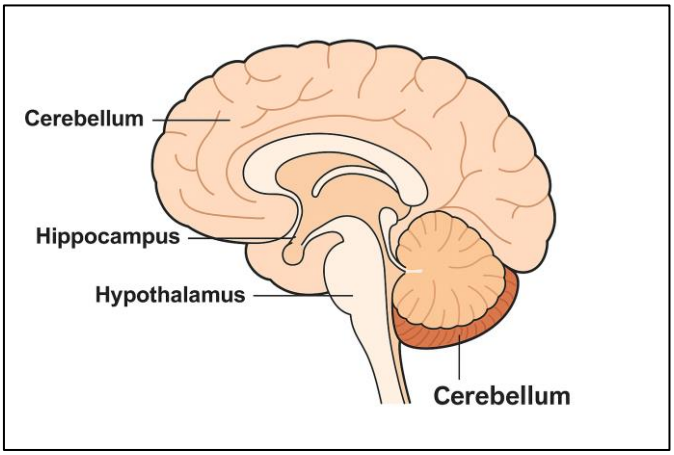

Figure 5: Brain regions influenced by GH/IGF-1. Illustration of the human brain highlighting hypothalamus, hippocampus, frontal cortex, and cerebellum as main sites of GH/IGF-1 action associated with cognition, learning, memory, and motor control

Source: Adapted from Tang *et al.*, 2022

In addition, ghrelin, a peptide hormone produced in the stomach and hypothalamus, emerged in the early 2000s as a potent stimulator of GH secretion through the growth hormone secretagogue receptor (GHSR). Ghrelin integrates signals of energy balance and nutritional status with somatotrophic function, linking the gastrointestinal tract and the brain (Muller *et al.*, 2009; Medeiros *et al.*, 2022).

Other modulators include sex steroids, pubertal rise in GH, glucocorticoids with context-dependent effects, thyroid hormones synergistic with GH for growth, and nutritional factors such as amino acids (arginine), glucose, and free fatty acids. Collectively, these influences explain why GH secretion is highly sensitive to age, sex, body composition, and nutritional state (Muller *et al.*, 2009; Medeiros *et al.*, 2022).

3.8. Advances and future perspectives

The advent of long-acting GH (LAGH) offers promise for improving adherence, a crucial determinant of treatment efficacy. However, more real-world data are required to determine whether simplified regimens translate into superior neurocognitive and psychosocial outcomes. Similarly, while recombinant DNA technology has ensured the safety and availability of GH worldwide, further innovations such as personalized dosing guided by pharmacogenomics and integration of

digital health tools may optimize long-term care (Muller *et al.,* 2009; Medeiros *et al.,* 2022).

3.9. Research Gaps

Critical gaps remain in understanding the full neurodevelopmental impact of GHD. Few studies have incorporated standardized neuropsychological batteries alongside imaging, metabolic, and endocrine assessments. Longitudinal research from early childhood to adulthood is needed to disentangle whether cognitive deficits are direct consequences of GH deficiency, secondary to metabolic disturbances, or influenced by environmental and educational factors. Clarifying the roles of GH versus IGF-1, and their interaction with sleep and circadian regulation, represents another important research priority (Muller *et al.,* 2009; Medeiros *et al.,* 2022).

3.10. Clinical Implications

The available evidence suggests that GHD in childhood should not be managed solely through endocrinology. Effective care requires multidisciplinary teams including pediatric endocrinologists, neurologists, psychologists, neuropsychologists, and educational specialists (Muller *et al.,* 2009; Medeiros *et al.,* 2022).

This integrative approach enables the early detection of learning difficulties, targeted interventions, and psychosocial support, all of which can be provided alongside GH replacement. In practice, the ultimate goal is not only to normalize height but also to optimize brain development, quality of life, and future independence (Muller *et al.,* 2009; Medeiros *et al.,* 2022).

3.11. Articles 2024 to 2025.

1. GH as an adjuvant in low responders to ovarian stimulation (IVF/ICSI)

The presence of GH receptors in granulosa and theca cells supports the rationale for the adjuvant use of GH in low responders in assisted reproduction. ESHRE guidelines suggest that, although there are possible gains in outcomes such as live birth rates in poor responders, the evidence is still limited for routine recommendation (ESHRE, 2020). Meta-analyses indicate a trend toward improvements in oocyte retrieval, better-quality embryos, implantation/clinical pregnancy rates, and endometrial thickness, but highlight heterogeneity and risk of bias (Yang *et al.,* 2020; Lin *et al.,* 2021; Sood *et al.,* 2021).

Recent studies also explore the duration and timing of GH co-treatment, with no consensus on the route, dose, and schedule (Mohammadshirazi *et al.,* 2023). Practical conclusion: There is no consensus for routine use; it can be considered on a case-by-case basis in poor responders, reporting uncertainties, and monitoring outcomes (Bosch *et al.,* 2020; Sood *et al.,* 2021; Lin *et al.,* 2023).

2. Aesthetic use of GH: alleged benefits vs. real risks

Despite the interest in bodybuilding and aesthetic contexts, the use of GH outside of medical indications is not approved in Brazil and was banned by the CFM in 2023 (Capixaba Reporter, 2025; Bucis, 2025).

Although GH can reduce fat and alter body composition in specific scenarios, risks include insulin resistance/hyperglycemia, edema, carpal tunnel syndrome, arthralgias, blood pressure changes, and acromegaly with excessive use, in addition to potential proliferative stimulation that, in predisposed individuals, can increase the risk of neoplasia (Capixaba Reporter, 2025; Bucis, 2025).

Therefore, there is no safe shortcut to gaining mass/definition: the recommendation remains focused on safe and supervised practices (Capixaba Reporter, 2025; Bucis, 2025).

3. GH – Hormone for muscle mass

Growth hormone can be produced synthetically, but using it without medical supervision or a documented clinical need is illegal and potentially harmful. The safest and most effective way to increase GH is to stimulate the body's own production through three main pillars: exercise, adequate sleep, and balanced nutrition. Intense resistance exercise is one of the strongest natural triggers for GH release. Workouts that require high energy output, such as weight training or sprint intervals, stimulate protein synthesis and signal the pituitary gland to secrete more hormones (MundoBoaForma Team, 2021).

Short, high-intensity sessions that engage large muscle groups produce greater hormonal responses than long, low-intensity activities like endurance running. Quality sleep is equally important because the majority of daily GH secretion occurs at night, particularly during phases of deep sleep. Consistently sleeping for eight to ten hours allows the pituitary gland to maintain a strong secretion rhythm and supports muscle repair, while chronic sleep deprivation disrupts pituitary function and lowers natural GH levels (MundoBoaForma Team, 2021).

Nutrition provides the essential raw materials for hormone production. Certain nutrients, often referred to as GH secretagogues, enhance the pituitary's ability to release the hormone. Beneficial compounds include the amino acids arginine, glutamine, glycine, and branched-chain amino acids (BCAAs); the metabolite ornithine alpha-ketoglutarate (OKG); and minerals such as magnesium, zinc, chromium, and iodine, along with vitamins A, B5, B12, and folate. Botanical extracts such as *Tribulus terrestris*, *Griffonia simplicifolia*, and silymarin derived from milk thistle have also been investigated for their potential to support GH secretion.

Some athletes and bodybuilders misuse injectable GH in an attempt to accelerate fat loss or muscle gain. Experimental research shows that GH can redirect calories toward protein synthesis and reduce fat storage, and combined use with testosterone or other anabolic steroids may amplify these effects. However, GH's anabolic capacity is lower than that of testosterone, and although it does not undergo aromatization to estrogen, misuse of GH still carries significant risks, including metabolic disturbances and unpredictable long-term consequences (MundoBoaForma Team, 2021).

4. How to naturally increase your GH levels

The pituitary gland produces growth hormone (GH), a potent anabolic hormone that regulates cell growth, tissue repair, and metabolism in humans and other vertebrates. GH supports muscle development, promotes fat mobilization, and helps maintain overall metabolic balance. The body's own production of GH can be enhanced naturally, without synthetic hormones or supplements, by adopting specific lifestyle and nutritional strategies (MundoBoaForma Team, 2021b).

Approximately 75% of daily GH secretion occurs during deep sleep, making consistent, restorative rest one of the most effective ways to stimulate natural hormone release. Sleeping eight to nine hours per night provides the best conditions for GH production, while sleep deprivation, even when followed by extra rest on weekends, cannot fully restore normal output. Deep and uninterrupted sleep not only boosts GH secretion but also aids muscle recovery and training adaptation (MundoBoaForma Team, 2021b).

High-intensity resistance exercise is another powerful natural trigger for GH release. Workouts that require significant energy expenditure, such as weight training or sprint intervals, stimulate protein synthesis and signal the pituitary gland to secrete more hormone. Short, high-intensity sessions that engage large muscle groups generate stronger hormonal responses than long, low-intensity activities like endurance running. Intense workouts should be limited to about 45 minutes to avoid excessive cortisol, a stress hormone that can counteract GH, and session duration can be gradually increased as the body adapts (MundoBoaForma Team, 2021b).

Frequent consumption of sugary foods causes rapid insulin spikes, which suppress both GH and testosterone. Reducing intake of refined carbohydrates lowers insulin and somatostatin activity, two factors that inhibit GH secretion, and supports a more favorable metabolic profile. Adequate intake of specific amino acids, including lysine, arginine, glutamine, glycine, and ornithine, has also been linked to greater GH release. Research shows that combining lysine and arginine before training can enhance GH output, while two to five grams of glutamine after exercise or before bedtime can produce measurable increases. Arginine is particularly effective when taken shortly before workouts (MundoBoaForma Team, 2021b).

Short bursts of vigorous activity, such as high-intensity interval training, elevate heart rate and recruit fast-twitch muscle fibers, both of which naturally boost GH secretion. A 20-minute session once or twice per week can meaningfully increase circulating GH levels. A diet rich in high-quality protein provides the amino acids needed for GH synthesis, while limiting refined carbohydrates helps prevent insulin peaks that interfere with hormone production. Nutrients such as choline and Gamma-Aminobutyric Acid (GABA) may further support GH release. Melatonin promotes GH secretion by improving sleep quality, and vitamin D obtained through safe sun exposure and foods such as cold-water fish, egg yolks, and mushrooms plays a synergistic role by enhancing both GH and testosterone activity. Short-term fasting followed by controlled eating windows can also elevate GH levels. Even a 16-hour overnight fast has been shown to increase GH secretion, although prolonged fasting should be approached carefully to avoid muscle loss (MundoBoaForma Team, 2021b).

Maintaining a healthy body is equally important. Excess body fat is associated with elevated insulin, which inhibits GH production. Regular physical activity and balanced nutrition help reduce fat mass, lower insulin levels, and naturally stimulate GH release. Simple lifestyle habits, including regular laughter, have also been linked to higher GH output, likely by reducing cortisol and stress. Supporting liver health is another key factor, as the liver converts GH into insulin-like growth factor 1 (IGF-1), the primary mediator of GH's anabolic effects. A diet rich in leafy greens and limited in alcohol, sugar, and saturated fats helps maintain optimal liver function and hormone activation. Natural strategies such as restorative sleep, structured exercise, balanced nutrition, intermittent fasting, and stress management provide safe and effective ways to enhance GH production, offering long-term metabolic and musculoskeletal benefits without the risks associated with synthetic hormone use (MundoBoaForma Team, 2021b).

3.12. CONCLUSION

Growth hormone (GH) plays a crucial role in both physical growth and brain development. Children with GH deficiency can experience structural and functional changes in the brain, such as an altered hippocampus, reduced white matter, and weaker connectivity, leading to problems with learning, attention, and executive functions. Recombinant GH therapy enhances growth and may improve cognitive outcomes, and newer long-acting formulations could support treatment adherence, though their long-term neurodevelopmental effects remain uncertain. Since responses vary, early diagnosis, personalized therapy, and multidisciplinary follow-up are vital. Future research

combining endocrine, cognitive, and imaging data is necessary to better understand how GH supports neurodevelopment and to optimize treatment.

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