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Growth hormone deficiency in the neurocritical patient. Traumatic brain injury perspective

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ABSTRACT

Growth hormone (GH) is synthesized in the anterior pituitary, but its production and release are controlled by two neurohormones found in the hypothalamus: somatostatin and growth hormone-releasing hormone (GHRH). GH supports bone growth, regeneration of neurons, astrocytes, endothelial cells, oligodendrocytes, and even neuronal myelination. It is also responsible for stimulating the growth and differentiation of cells from different tissues and cell types, thereby contributing to protein synthesis. Original research papers, case reports, and case series on GH deficiency among neurocritical patients were thoroughly examined in this review. After extensive study, 13 articles were selected for the analysis. Traumatic lesions are defined by distortion of the brain tissue and subsequent biochemical modifications, which can affect GH secretion. The majority of researchers identified fractures, trauma, and bleeding as the mechanical causes of GH deficiency, and subarachnoid

haemorrhage (SAH) or traumatic brain injury (TBI) as the etiology. The dysregulation of certain other hormones, including ACTH, Cortisol, Gonadotropin, Prolactin, FSH, TSH, Testosterone, and Hydrocortisone is also related to GH insufficiency. Growth hormone deficiency can cause complications such as hypothyroidism, hypotension, hypoxia, adrenal insufficiency, electrolyte imbalance, hyperprolactinemia, depression, anxiety, concussions, seizures, vomiting, and loss of consciousness. According to previous studies, GH insufficiency is significantly affected by age, body mass index (BMI), pituitary dysfunction, and hypogonadism. GH treatment is widely used in patients with GH deficiency, as it has more benefits than harm. The GH dose should be individualized to minimize side effects and maximize clinical efficacy.

Introduction

Growth hormone (GH) is produced in the adenohypophysis and stimulates cell growth and differentiation. Its synthesis and release are influenced by two hormones: growth hormone-releasing hormone (GHRH), which stimulates the synthesis and release of GH, and somatostatin, which inhibits GH and acts as a negative feedback mechanism. It has been established that blood levels of this hormone are at their maximum during sleep. [1, 2] Somatotropic cells produce GH in the lateral regions of the adenohypophysis. This hormone is a protein that weighs approximately 22,650 Da and consists of 191 amino acids. GHRH and somatostatin, two neurohormones found in the hypothalamus, are necessary for the production and release of these hormones. While the second is inhibiting, the first has stimulating quality. [3] Considering that various trauma-related processes, such as inflammatory or ischemic damage, might harm the brain parenchyma, brain trauma can change the metabolism of GH. [4-6] Traumatic brain injuries can deform brain tissue and subsequently generate biochemical changes. The ischemic changes that occur during brain injuries cause hormonal loss, mainly of somatotropin and gonadotropin; thus, there is an alteration in GH metabolism. In the present article, we review the role of growth hormone in patients with traumatic brain injury.

Physiology

GH excretion is pulsatile and an ultrasensitive test that can be used to measure blood levels. The somatostatin-induced inhibition was reduced to control these pulses. It was discovered that on an average, serum GH during the night oscillates between 1.0±0.2 ng/ mL, while daytime concentrations are on average 0.6±0.1 ng/ mL in adults. These levels may be lower in adults with obesity, older adults, and neonates. Therefore, serum GH measurement should be performed in a 20-minute sample for 24 h, which would allow accurate evaluation of serum GH concentrations. [7, 8] The maximum serum GH concentration ranges from 4.3±0.7 ng/ mL at night to 2.7±0.5 ng/ mL during the day, with the highest GH excretion peak occurring 1 hour after the onset of deep sleep. Physical activity, trauma, and septic conditions increased GH secretion by 20–30 ng/mL. [9] GH, in contrast to other hormones secreted by the pituitary gland, affects every cell in the body.

The proliferation and differentiation of cells from diverse tissues and cell types are stimulated by this hormone. It also increases the risk of developing diabetes by lowering peripheral tissue glucose absorption, enhancing liver glucose release, and subsequently increasing insulin secretion. [3] Its role in astrocyte, endothelial, oligodendrocyte, and neuronal myelination regeneration has been investigated. Additionally, it has been linked to various activities, including neuronal migration and survival. [1, 10] Other regulators have been identified, such as IGF-1, which may both mediate the activities of GH in the periphery and limit its secretion. Hormones such as leptin can stop GH production. The intestinal peptide ghrelin, which is expressed in the anterior pituitary gland, has also been linked to these associations. This peptide is synthesized in the stomach and is important because it is a nutritional regulator of GH secretion that maintains blood glucose levels during starvation. [7]

When GH binds to a particular homodimer receptor, which is mostly found in the liver, it leads to intracellular signaling by activating the JAK/STAT pathway through the phosphorylation cascade. Its major effect is the promotion of hepatic production and the release of IGF-1, which aids in cell division and development. [11]

Pathophysiology

Traumatic lesions initiate an inflammatory cascade marked by the presence of inflammatory cytokines and excitatory neurotransmitters that change the balance of calcium and other electrolytes.

Inflammatory compounds are released into the extracellular medium, causing internal self-destruction pathways, which are represented by proteases and caspases that break down cytoskeleton proteins and irreversibly activate programmed cell death. [4, 12, 13] Although the precise etiology of hypopituitarism following traumatic brain injury is unclear, several pathogenic pathways have been suggested as the cause of this dysfunction. [5, 14] Growth hormone deficiency can cause some complications in patients, such as hypothyroidism, hypotension, hypoxia, adrenal insufficiency, electrolyte imbalance, hyperprolactinemia, depression, anxiety, concussions, seizures, vomiting, abnormal scan results, and loss of consciousness. According to previous research, GH insufficiency is significantly affected by age, BMI, pituitary dysfunction, and hypogonadism. [13, 15] Due to the pituitary's physical position, these individuals have ischemic alterations. These changes result from a decrease in cerebral perfusion, which is ascribed to the fragility of the arteries that supply this region. [12] The dysregulation of certain other hormones, including ACTH, Cortisol, Gonadotropin, Prolactin, FSH, TSH, Testosterone, and Hydrocortisone, etc., is also a symptom of GH insufficiency.

Diagnosis

Since GH deficiency might be mistakenly identified in individuals who simply have non-specific clinical symptoms, including lethargy, weakness, and obesity, an examination for GH deficiency should be taken into consideration in patients with illnesses that potentially cause it. Arginine, glucagon, levodopa, and clonidine stimulation tests, as well as the insulin tolerance test (ITT) and growth hormone-releasing hormone (GHRH), are used to identify GH insufficiency because GH is produced in bursts. The fundamental idea behind the GH stimulation test is to repeatedly measure blood GH levels following the introduction of a drug that quickly stimulates GH. The patient's GH reaction was then deduced from the maximum GH levels of the samples. [16, 17] Despite being the gold standard test for GH deficient diagnosis, ITT has been contraindicated in elderly patients, patients with a history of epilepsy, and patients with cardiovascular disease due to its hazards of hypoglycemia. ITT is particularly challenging to duplicate because healthy people respond differently to ITT on different occasions. [17] Most individuals with idiopathic child-onset GH insufficiency exhibit normal GH secretion when reassessed in adulthood. GH stimulation tests do not need to be repeated in patients with structural problems that cause GH deficits, such as tumors, surgery, radiation, and genetic abnormalities, because these conditions do not improve maturity. [18, 19] GH stimulation tests can be skipped if the patient has structural hypothalamic-pituitary conditions, genetic conditions that affect the hypothalamic-pituitary axis, structural lesions in the hypothalamus or pituitary gland, abnormally low levels of three or more pituitary hormones, and low IGF-1 levels (at least 2.0 standard deviations below normal). [17, 20-22]

Management

Patients with GH deficits identified by GH stimulation testing are advised to begin GH replacement treatment. Given that the adverse effects are dose dependent, patients should begin treatment with modest dosages. Typical adverse effects include fluid retention, arthralgia, muscular soreness, sensory abnormalities, carpal tunnel syndrome, sleep apnea, sleep difficulties, and dyspnea. Patients who are elderly, fat rich, or female are more likely to experience adverse effects, but they go away when the dose is reduced. Based on the dosage guidelines for children, the GH doses for adults were first calculated based on body weight. However, when dosage recommendations are made individually rather than solely based on weight, adverse effects are reduced by half. [23-25] Age causes a reduction in GH production; therefore, elderly people are more likely to experience adverse GH effects. Therefore, therapeutically acceptable GH levels are lower in the elderly and greater in the younger population. 0.2 to 0.3 mg/day (0.8 to 1.2 IU/day) is a good beginning dosage for those between the ages of 30 and 60. While a greater dose of 0.4 to 0.5 mg/day (1.6 to 2.0 IU/day) is possible for those under the age of 30, those over 60 should start with a dose of 0.1 to 0.2 mg/day (0.4 to 0.8 IU/day) and gradually raise it over time. The dosage should be increased by 0.1 to 0.2 mg/day (0.4 to 0.8 IU/day) monthly or bimonthly, and the maintenance level should be determined based on an evaluation of the patient's clinical response, side effects, and the normal range of IGF-1 levels for the patient's age group. Although normal IGF-1 levels

are targeted, evidence remains unclear. Clinical responses can usually be observed after 6 months of treatment. [26, 27] Females typically exhibit greater levels of GH resistance, necessitating larger initial and ongoing dosages. In the liver, where 85% of serum IGF-1 is produced, estrogen promotes suppressor of cytokine signaling 2 (SOCS2), a non-competitive suppressor of GH. IGF-1 is suppressed by oral estrogen; therefore, females need to take more GH to maintain their levels at the same level. Indicators of body fat, low-density lipoprotein cholesterol, and bone turnover in women are less affected by GH, even at the same IGF-1 levels. GH levels need to decrease when oral estrogen is switched to transdermal estrogen. [28-31]

Follow up

The adequacy of GH dosage, including an assessment of the patient's clinical response, side effects, and IGF-I levels, should be checked monthly or biweekly during the adjustment phase. IGF-1 levels should be checked every six months once the maintenance level has been established. Fasting blood sugar and cholesterol levels should be checked annually, and if the first bone mineral density is abnormal, it should be checked every 1.5 to 2 years. Additionally, quality of life and waist size need to be assessed. After GH is administered, the thyroid or adrenal hormone dosage that the patient is already receiving should be changed. These suggestions are supported by the actual data. Although it is not clear exactly how long GH should be administered, therapy can be stopped if there is no noticeable improvement from GH replacement after at least a year. [26, 28] The freshly created long-acting GH is designed to be taken weekly or monthly rather than daily. Because it lessens the bother and discomfort associated with regular GH injections, long-acting GH may be more effective in improving compliance. A recent meta-analysis found that the effectiveness and safety profiles of daily and long-acting GH were comparable. However, in children with GH deficiency who received long-acting GH, IGF-1 levels were noticeably increased. The effects of peak and trough GH and IGF-1 levels on efficacy and safety, modification of the dose, assessment of IGF-1 levels, and assessment of the long-term cost-effectiveness of daily and long-acting GH preparations should be the subject of future studies. [32, 33]

Future research

In an effort to increase adherence to therapy in GH-deficient individuals, several methods have been developed and researched. These methods range from creating devices that make GH administration less uncomfortable to altering the GH molecule and prolonging its action in the body. Future research should focus on the development of devices for better GH delivery. To replicate pulsatile GH secretion via microfluidic devices, micro total analysis systems (TAS) and microelectromechanical systems (MEMS) have been developed. [34] MEMS are still in the early phases of research and may be used for one day to treat GH insufficiency. To ensure continuous delivery of GH in a pulsatile manner, it is necessary to combine biological alterations of GH to improve its solubility and MEMS. A device that reacts to physiological stimuli and administers GH in a pulsatile fashion is necessary to provide viable MEMS for GH treatment. MEMS are appealing for biological applications owing to their ability to continuously distribute medicine and hence avoid peak-valley oscillations. With innovations based on diagnostics, medical wearables, digital health, and innovative medication delivery methods, MEMS offer significant translational promise. [34-36] Chronic disorders such as type 1 diabetes are successfully treated using microfluidics for medication delivery. Microfluidics-based GH delivery devices are now on the market and are being evaluated for adherence, with better outcomes than routine injections. EasypodTM is an automated electronic injection device for the delivery of GH based on MEMS, providing benefits for the patient as it causes less pain and has an electronic setup and dosage for proper GH administration, as well as digital follow-up of the patient's injections and information about treatment adherence to the doctor. Great strides have been made in the use of cadaveric GH to rGH and EasyPodTM, providing patients with a variety of therapeutic options. [37, 38].

Conclusion

It has been observed that traumatic brain injuries can lead to endocrine dysfunction that can lead biochemical changes; permanent lesions have been explained due to the alteration in the shape and function of the blood vessels, finding a compromise in cerebral irrigation; as a result of this and taking into account the anatomical location, the pituitary

gland is an organ susceptible to ischemic damage. Patients with GH deficiency require GH replacement therapy, and age and sex are two important factors that cause GH production. Females typically exhibit greater levels of GH resistance, necessitating larger initial and ongoing dosages. Future research needs to be conducted to develop devices for better GH delivery. Moreover, more research is required to develop innovative treatment strategies for GH-IGF axis diseases and other types of short stature for a better understanding of their pathogenesis.

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