HISTORY OF GROWTH HORMONE: ANIMAL TO HUMAN

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HISTORY OF GROWTH HORMONE: ANIMAL TO HUMAN

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EDITORIAL
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Editorial: History of Growth Hormone: Animal to Human

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Editorial on the Research Topic

History of Growth Hormone: Animal to Human

INTRODUCTION

Fascination with extremes in the size of man or animals (as well, amazingly, of plants) has a long history stretching to Antiquity. Giants are described in the Bible (Goliath and the Nephilim), as well as portrayed in classical art, such as The Colossus of Goya (1808-1812), displayed in the Prado Museum. At the other extreme, the same museum portrays little people, Las Meninas by Velazquez. There is the well-known American, General Tom Thumb, who likely had GH deficiency (GHD) and was a successful member of the PT Barnum Circus.

The striking clinical picture of *acromegaly* with the suggestion of a pituitary mass led to studies in the 19th and 20th centuries and the realization that a pituitary substance was responsible. Extraction and purification of a growth-promoting factor within the anterior pituitary was enabled by the development of successful hypophysectomy in animals. That was followed by the ability to purify various pituitary factors and administer them to reverse the post-hypophysectomy biological state. Additionally, it was important to develop sensitive bioassays. Using a cartilage bioassay, Knobil and colleagues demonstrated species specificity of primate and sub-primate GH (1).

HUMAN GROWTH HORMONE TREATMENT

After hGH was purified, administration to an adolescent was initiated in 1956 by Raben and his associates (2). By the mid-1960's, many children with GHD were being treated with hGH supplied by the NIH-funded National Pituitary Agency which coordinated the extraction and purification of hGH from cadaveric pituitaries (3). As the number of children with GHD increased and other indications for treatment of short children developed, the need for more hGH was apparent. At the same time, however, there was the realization that human pituitary glands were contaminated with the agent responsible for the nearly uniformly fatal neurodegenerative condition, Creutzfeldt-Jacob Disease (CJD). This quickly led to cessation of the production and administration of pituitary hGH.

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Fortuitously, we were at the dawn of the recombinant DNA era when an essentially unlimited supply of highly pure biosynthetic rhGH became available.

GROWTH HORMONE DEFICIENCY

Detailed information regarding the diagnosis, treatment, and long-term outcomes is provided in the second manuscript in this Research Topic by Professor Ranke. Diminished GH production is primarily due to developmental abnormalities of the hypothalamic-pituitary area. Characterizing the action of GH has led to extensive examination of the GH-dependent peptides, IGF-I and IGFBP3, but beyond the scope of this presentation.

The incidence of diagnosed GHD has increased in parallel to the almost limitless availability of rhGH. That has enabled treatment regimens based on clinical need rather than to a constrained supply of pituitary-extracted hGH. Ranke describes the range of findings and the laboratory studies required to confirm the suspicion of impaired GH production. Decreased height velocity of children in infancy and early childhood may be difficult to ascertain, so the occurrence of hypoglycemia associated with other pituitary hormones must be included in the assessment. IGFBP3 measurements, which are less influenced by nutrition or illness than of IGF-I, may be used. Imaging studies of the hypothalamic-pituitary anatomy are particularly valuable in the very young child. During childhood, careful determination of diminished height velocity with ample interval between measurements is a central tenet. In addition to the auxologic findings, many different pharmacologic "provocative" tests evaluating GH secretion have been used to confirm GHD. As the child's age approaches pubertal onset, but remains prepubertal, the impact of relatively low levels of sex steroids may impair GH secretion and yield results falsely low stimulated GH results suggesting impaired GH secretion. Auxologic data remain important at this stage but must be considered in light of pubertal status similar to the pharmacologic test results.

TREATMENT OF CHILDREN WITH GHD

Daily subcutaneous doses of rhGH at ranges of 25-43 μg/kg/day are used, bearing in mind adherence to this regimen to achieve optimal growth. Determination of the response to rhGH treatment is largely based on height velocity during treatment comparing growth data from large pharmaco-epidemiologic studies. Varied auxologic parameters have been inserted into sophisticated GH-treatment-associated prediction models that permit guidance into characterizing the growth of an individual child. A diminished response relative to prediction should lead to an overall examination of the adherence with the treatment program.

Increased adult height with treatment of GHD has been possible over the past several decades. Early diagnosis, aggressive treatment at that time, more sophisticated management of growth in the peri-pubertal period, and availability of rhGH until growth cessation have allowed children with GHD to achieve adult heights close to the mid-parental height.

In addition to an ongoing assessment of the near adult height data, there is the scrutiny of the long-term safety of GH treatment. The recognition of the devastating development of Creutzfeld-Jacob Disease in association with the use of cadaveric hGH has sensitized the current users of rhGH to potential long-term rhGH-related adverse events and the need to search for evidence of rhGH-related adverse events, such as neoplasia and cardiovascular disease.

Other indications approved for treatment with recombinant GH (rhGH) are listed below and discussed in the manuscript by Graber et al. outlining the studies that led to the approval of these indications. Children with these varied diagnoses do not have GHD, but rather have at least partial resistance to the action of hGH, perhaps without adequately increasing its production to overcome the resistance (4). To date, the FDA has approved 8 conditions in children and adolescents for which rhGH is considered both safe and effective (table):

Diagnosis	Year of FDA Approval
GH deficiency	1985
Chronic renal insufficiency	1993
Turner syndrome	1996
Prader-Willi syndrome	2000
Small-for-gestational age without catch-up growth	2001
Idiopathic short stature	2003
SHOX-deficiency	2006
Noonan syndrome	2007

LONG-ACTING GH

rhGH has been administered to patients as daily subcutaneous injections. This requirement leaves adherence to such regimens as an important variable when judging efficacy of treatment. Indeed, diminished adherence could falsely suggest that a given dose of rhGH was inadequate or even that a child with a given diagnosis was being treated inappropriately when growth was inadequate. The currently available LAGH preparations are in various stages of assessment (5) and it is likely that their use, when approved, will diminish the non-adherence issue.

GROWTH HORMONE DEFICIENCY IN CHILDHOOD CANCER SURVIVORS

Childhood cancer survivors (CCS) are afflicted with diverse morbidities of the hypothalamic-pituitary axis due to direct effects of tumors, operative intervention, drug treatments, and radiation therapy, with radiotherapy dosage affecting the time to and intensity of the appearance of the acquired GHD. Pollock and Cohen describe the diagnosis of GHD and treatment with

exogenous rhGH treatment in this population, as well as the anabolic and quality of life benefits of hGH.

Growth hormone deficiency gradually develops over post-treatment years in the setting of the ongoing risks of tumor recurrence and new secondary neoplasms. Given the mitogenic potential of rhGH and IGF-I, one must continue to assess the impact of treatment with rhGH in the survivors. There does not appear to be an increase in GH-induced tumor recurrence or secondary neoplasia, however longer term studies are needed. While the greatest tumor recurrence has been for craniopharyngioma, this is without a difference in rhGH exposure, nor an association with GH dosage (6). An increased incidence of meningiomas as secondary neoplasms in rhGH-treated patients is confounded by the strong association of meningiomas with prior brain irradiation. Thus, prior cancer therapy is not an absolute contraindication to hGH therapy. The type of primary cancer and whether the tumor occurs in the setting of a genetic syndrome associated with development of neoplasms may alter the risk-benefit ratio of rhGH therapy, although more data are needed. This is a many decades task.

AUTHOR CONTRIBUTIONS

All authors contributed to the drafting and editing of this editorial. All have approved the final version.

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REVIEW
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Human Growth and Growth Hormone: From Antiquity to the Recominant Age to the Future

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Since antiquity Man has been fascinated by the variations in human (and animal) growth. Stories and art abound about giants and little people. Modern genetics have solved some of etiologies at both extremes of growth. Serious study began with the pathophysiology of acromegaly followed by early attempts at treatment culminating in modern endoscopic surgery and multiple pharmacologic agents. Virtually at the same time experiments with the removal of the pituitary from laboratory animals noted the slowing or stopping of linear growth and then over a few decades the extraction and purification of a protein within the anterior pituitary that restored, partially or in full, the animal's growth. Human growth hormone was purified decades after those from large animals and it was noted that it was species specific, that is, only primate growth hormone was metabolically active in primates. That was quite unlike the beef and pork insulins which revolutionized the care of children with diabetes mellitus. A number of studies included mild enzymatic digestion of beef growth hormone to determine if those "cores" had biologic activity in primates and man. Tantalizing data showed minimal but variable metabolic efficacy leading to the "active core" hypothesis, for these smaller peptides would be amenable to peptide synthesis in the time before recombinant DNA. Recombinant DNA changed the landscape remarkably promising nearly unlimited quantities of metabolically active hormone. Eight indications for therapeutic use have been approved by the Food and Drug Administration and a large number of clinical trials have been undertaken in multiple other conditions for which short stature in childhood is a sign. The future predicts other clinical indications for growth hormone therapy (and perhaps other components of the GH?IGF-1 axis), longer-acting analogues and perhaps a more physiologic method of administration as virtually all methods at present are far from physiologic.

Keywords: growth, growth hormone, species specificity, recombinant DNA technology, FDA indications, long-acting growth hormone

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INTRODUCTION

Fascination with extremes in the size of man has a long history, even stretching to Antiquity. Giants such as the biblical Goliath confronting David, the Colossus in Goya's 1808-1812 masterpiece, and the Irish Giants are examples of great height growth, while the diminutive man (likely a person with achondroplasia) in the marvelous 17th century painting of Velazquez, *Las Meninas* and Tom Thumb, a young man with presumed growth hormone deficiency in P.T. Barnum's shows in the mid-19th century are among several examples of extreme short stature.

Furthermore, more than a century has gone by in which scientists have attempted to understand the metabolic pathways that bring about the wide variations in human growth. One has come from a time of thoughtful animal experimentation to highly sophisticated molecular tools to begin to understand growth. We describe some of the scientific work that has enabled us to begin to address the very basics of the hormonal regulation of growth.

OVERGROWTH

Antiquity

The Old Testament (New International Version) notes the story of David and Goliath in I Samuel 17 (**20-58**):"As the Philistine moved closer to attack him, David ran quickly toward the battle line to meet him. Reaching into his bag and taking out a stone, he slung it and struck the Philistine on the forehead. The stone sank into his forehead, and he fell face down on the ground". Goliath had gigantism likely secondary to a pituitary tumor that had grown out of the sella turcica to press upon the optic chiasm and cause bitemporal hemianopia with Goliath having tunnel vision (1). The clinical picture of acromegaly may include significant cardiopulmonary disease and osteoarthritis that may be crippling and could have prevented Goliath, with limited mobility, from avoiding the spherical projectile. Additionally, and certainly in the untreated state, there may be skeletal fragility, with the detrimental impact of excessive growth hormone and IGF-1 upon the craniofacial and cervical vertebral skeleton (2) Height estimates for Goliath have varied considerably from four cubits and a span (6 feet 9 inches, ~2.06 m) to 6 cubits and a span (9 feet 9inches, ~2.97 m). The older manuscripts, namely the Dead Sea Scrolls of Samuel, seem to lean toward the lower height measurement (3). Additionally, Goliath or other giants are described as being from the city of Gath (1 Samuel 17.4). In a different war with the Israelites (1Chronicles20:4-8) they were killed by David or by David's brother and his servants. These giants were said to be descended from a clan (from Gath) of men of large size (4). This raises the question of there being the presence of genetic regulation of the excessive growth hormone production in these men, as has been described elsewhere (see below; Irish Giants). There is mention of the presence of extra digits on hands or feet raising the question of the diagnosis of Bardet-Biedl syndrome, which is inherited closely to an area on chromosome 11q.13 near the gene associated with the inherited pituitary tumor in the Irish giants (Increased population risk of AIP-related acromegaly) (5). On the other hand, their recognition as being a group of vaunted warriors might speak against a growth hormone etiology with all of the health abnormalities of acromegaly.

Pre-20th Century

In the early 19th century Goya painted *The Colossus*, a dark portrait of a giant towering over a landscape with multiple people in awe of someone of such size; this is displayed in Museo del Prado in Madrid. The medical diagnosis present in this muscular, powerful-appearing man, could include late onset of excessive growth hormone secretion, perhaps from a pituitary tumor, but in a man with abundant androgen production that persists. Alternatively, the painting represents the wishful depiction of a man who has risen to protect the Spaniards from the invading Napoleonic forces during the Peninsular Wars.

The importance of the pituitary for excessive growth was recognized by the French physician, Pierre Marie, who associated the clinical signs and symptoms of acromegaly with an enlarged sella turcica and pituitary tumors (6). Familial gigantism and acromegaly is a fascinating story with roots in the mid-18th century in Ireland (Irish giants). The Irish Giant was a man who was 7 feet 7 inches (2.31 m) tall, named Charles Byrne who achieved fame because of that height, but who died of tuberculosis and chronic alcoholism. His skull was later examined by Harvey Cushing who made the posthumous diagnosis of a pituitary tumor.

Marta Korbonits and co-workers have nicely summarized the story of the Irish Giant in its historical context and defined the molecular defect in the aryl hydrocarbon-interacting protein gene (*AIP*) that causes excessive growth hormone secretion before pubertal maturation and epiphyseal closure, hence gigantism and later acromegaly (7). They studied the DNA of Charles Byrne, 1761-1783, and from other giants from four Northern Irish families. The AIP mutation was found in 10 individuals with growth hormone-secreting adenomas; 8 of 10 presented with childhood-onset disease, and thus excessive height. This mutation was not found in other patients with growth hormone-secreting adenomas from other areas of Ireland. They estimated that the mutation positive pedigrees shared a common ancestor who lived about 2500 years ago (7).

UNDER-GROWTH

Additionally, there have been many descriptions of subjects with severe growth impairment (8). Adelson relates the story of the sexual ateliotic dwarf (old term describing one not yet achieving perfection; in addition the term "dwarf" is now considered pejorative by some (9) and we shall use "little person"). Better known as General Tom Thumb, Charles Sherwood Stratton was born in Connecticut in 1838. –and lived to age 45 years dying of a stroke. His growth pattern from infancy mirrored that of a growth hormone deficient individual. His growth ceased by the middle of the first year of life, not to start growing again until puberty. His adult height was 101.4cm (about 3.5 feet). His

appearance and doll-like facies suggest that he had isolated growth hormone deficiency and would have responded well in the present to exogenous growth hormone. He was a long time financially successful member of the P.T. Barnum Circus and was married to a growth hormone deficient woman, with whom he had one child. He traveled the world meeting royalty and President Lincoln.

The lives of little people are explored in great detail by Betty M. Adelson, *The Lives of Dwarfs* (10) [www.hpb.com/products/the-lives-of-dwarfs]. In a masterpiece, *Las Mininas*, produced by Diego Velazquez in the mid-17th century, two little persons are depicted in a remarkable painting of the court of King Phillip IV of Spain with two ladies in waiting and two little persons, one of whom apparently has achondroplasia.

FINDING THE GROWTH-PROMOTING AGENT(S) IN THE ANTERIOR PITUITARY

The presence of a growth-promoting factor in the hypophysis, however, was not demonstrated until Aschner in 1909 employed a buccal approach to the sella to remove the pituitary in puppies. The experimental animals showed severely retarded growth, and poor survival (11). Contemporaneously, Crowe and co-workers found consistently diminished growth in puppies with only partial surgical extirpation of the pituitary or of its anterior lobe (12). By careful postmortem examination they were able to assess the completeness of hypophysectomy and to rule out complicating cerebral injury, hemorrhage, or infection. The older dogs whose pituitaries were completely removed died within 5 days, but some of the puppies remained alive for as long as 20 days; they likely had secondary adrenal insufficiency. Importantly, removal of the posterior lobe had no effect on growth.

By 1912 Aschner and colleagues had perfected the technique of total hypophysectomy and were able to observe cessation of growth in puppies after total hypophysectomy without injury to the adjacent areas of the brain, removing the uncertainty of whether the diminished growth was due to a factor within the pituitary or because of damage to brain structures surrounding the pituitary (13).

It was not until 1921 that a positive effect of the hypophysis on growth could be demonstrated. Evans and Long reported an increase in body weight of *intact* plateaued female rats over their litter mate controls following the intraperitoneal administration of an *aqueous* saline emulsion of bovine anterior pituitary lobes (14). Since murine bony epiphyses never unite, the rats did not have the features of acromegaly, as in the human. "Acromegaly" was first experimentally produced in dogs by Putnam and co-investigators by injection of a sterile aqueous anterior pituitary extract for a period of 14 months. Dogs that received this extract had an increased body weight, enlargement of the acral parts, and polyphagia (15). At autopsy, general splanchnomegaly and skeletal overgrowth with hyperostoses were noted.

Although prior to 1930 certain effects of removal of the anterior pituitary upon growth in animals were known, the post-operative morbidity and mortality in dogs was high and there were no consistently effective methods for performing pituitary surgery in smaller animals. In a now classic series of experiments in 1930, P. E. Smith conclusively demonstrated the necessity of the hypophysis for *normal* growth using a reproducible ventral parapharyngeal approach to the sella in the rat that mitigated some of the injurious adverse events of the trans-buccal approach. Virtually complete cessation of growth followed ablation of the hypophysis or of its anterior lobe. If the posterior lobe alone were removed, there was no effect on growth. It is odd that the likely presence of diabetes insipidus didn't seem to alter growth. Daily anterior pituitary lobe homoeotransplants restored normal growth patterns-an increase in weight, body measurements and tail length-in the hypohysectomized animals. When injected intraperitoneally, a saline suspension of the bovine anterior lobes also produced physiologic growth, but had no effect on the atrophied reproductive organs (16).

EXTRACTION AND ISOLATION/ PURIFICATION OF GROWTH HORMONE

Attempts to purify and concentrate the active principle were rewarded with extracts of increasing biological potency with decreasing amounts of contaminating proteins. Although it was clear that the pituitary in some manner controlled growth, since the growth rate could be altered experimentally by pituitary manipulation, no one had isolated a single chemical substance with the specific function of growth promotion. In fact, there were many who believed that such a process as complex as growth could not be controlled by a single chemical factor. Bates and co-workers (17) expressed the general view that since the anterior lobe hormones act upon or through other endocrine glands whose target organs, thyroid, adrenals and gonads, produce hormones for healthy body maintenance, these target glands probably also participate in *normal* body growth. They argued that if one would replace the several hormonal deficits resulting from hypophysectomy, then the animal ought to return to a normal growth pattern. The experimental design used to prove this point consisted of groups of dwarf mice treated with "growth hormone" preparations (contaminated with prolactin and TSH, prolactin (heated to 37°C at pH7.5 to 8 for one hour to decrease the TSH activity and to denature the heat-labile "growth hormone"), and prolactin-free TSH preparations. Animals treated simultaneously with TSH and prolactin gained more weight than the combined weight gain of the TSH and prolactin-treated animals, demonstrating a synergistic effect of these hormones. Since the total weight gain was comparable to that of the rats receiving "growth hormone", the authors felt that growth was merely the synergistic effect of the pituitary hormones acting through their target organs. It should be noted that all of these experiments were performed with crude mixtures of hormones. Due to this and the fact that they employed mice with a genetically determined growth deficit, it is difficult to draw meaningful conclusions from this study.

In 1938 Evans and colleagues (18) developed a precipitation procedure for the isolation of growth hormone based on earlier methods which had given low yields and were grossly contaminated by lactogenic, thyrotrophic and gonadotrophic factors. Although the product had increased growth-promoting activity, it was accompanied by an increase in the activity of the contaminants. Several years later Frankel-Conrat and colleagues (19) used extraction in a cysteine-containing medium to prepare a more homogeneous product with greatly decreased contaminating hormones, but activity of the adrenals, thyroid and the preputial glands in the rat was still apparent. At approximately the same time Fevold and collaborators were able to prepare five anterior pituitary fractions rich in the individual hormonal activities, but none was chemically or biologically homogeneous (20).

Thus by the mid-1930's, the pathophysiology of acromegaly as well as the necessity of a factor from the anterior pituitary for physiologic growth were known. The next task was to purify and then identify that factor. Thus, hand-in-hand with devising a purification scheme was the related task of developing assays to help sort the growth-promoting factors from those that did not affect growth. The first usable assay was that of Evans and Long, noted above (14). Later, several modifications of this principle were tried using rats. Marx and co-workers developed a technique which measured the increase in body weight of either normal female rats at 5-6 months (weight plateaued) or rats hypophysectomized at 28-30 days of age. The logarithm of the daily dose (17 doses in 20 days) *versus* the body weight gain, a classical bioassay, was linear within a dose range of 0.25 to 4 mg for the normal rats and far more sensitive (0.03 to 0.48 mg) for the hypophysectomized animals (21).

Even greater sensitivity was found using the epiphyseal growth plate, for regressive changes were noted in the proximal epiphysis of the tibia in immature rats. The finding that these changes could be *reversed* by pituitary extracts formed the basis of a new and highly sensitive bioassay for growth hormone (22). Immature hypophysectomized female rats were injected intraperitoneally for 4 days with pituitary fractions in saline. The tibias were removed, sectioned in the sagittal plane and stained, before measuring the width of the proximal epiphyseal cartilage plate. The plot of the width *versus* the logarithm of the daily dose produced a straight line within a dose range of 5 to 200 μg of the "crude" material (22). This method was extended by Greenspan and co-workers who determined the conditions for maximal response and evaluated its specificity, sensitivity and accuracy (23).

This new procedure remarkably hastened the purification first of animal [bovine and porcine] growth hormones (18) and then the simian and human hormones (24). Next steps included the attempts to use bovine growth hormones (Bennett, and coworkers over a three week nitrogen balance study (25), or a longer trial over several months (26) or digests of them in the human (27, 28). Although some tantalizing data were obtained in multiple trials with a variety of enzyme digested growth hormones, no preparation unequivocally had reproducible activity in man. It should be remembered that porcine and bovine insulins were mainstays in the treatment of patients with diabetes mellitus at that time, so it is not surprising that such animal sources were first utilized.

SPECIES SPECIFICITY

The species specificity issue was evaluated by Knobil and co-workers who found that simian and later human growth hormones produced striking proliferative changes in the costochondral junctions of hypophsectomized Rhesus monkeys, but animal growth hormones did not; nor did they permit the retention of nitrogen in balance studies (29, 30). Other metabolic actions, including the auto-inhibition of secretion by pretreatment with simian growth hormone were noted in the intact and hypophsectomized Rhesus monkey [summarized in (31)]. The specificity of the human and simian activity resides in a single arginine residue in the simian (and human) growth hormone receptor and its cognate binding protein (32). The investigators concluded that incompatibility of Arg^{43} in the human GH receptor with His^{171} in non-primate GH is the major determinant of noted species specificity.

ACTIVE CORE HYPOTHESIS

Growth hormone is a pleotropic hormone with biological activity for carbohydrate, lipid and protein metabolism. However, unlike animal insulins or ACTH there was little if any biological activity in man. The biological data from primate growth hormones, the lack of activity of the animal hormones or mild enzymatic hydrolysis of the animal hormones in primates including man, and the activities of fragments of human or animal growth hormones in *some* animal bioassays led to an active core hypothesis (33). This property of species specificity was speculated to be due to a broad diversity in primary structure of growth hormone of various species, but all had the ability to form biologically functional peptides that only required a partial sequence. Once these were "unmasked", each could exert its specific biological activity. Thus the concept is that each of the growth hormones contains an "active core" (or cores) of amino acid sequence responsible for its multitude of biological actions (33). These studies far antedated recombinant DNA. It was speculated that if the cores were small enough one could synthesize the smaller peptides more readily than the full animal GH molecule and attain metabolic effects, perhaps including growth in man. Partial proof of that concept was the derivation of a peptide from bovine GH that induced glucose intolerance in fasted *ob/ob* mice (34). The same authors followed with a study of the cognate peptide *synthesized* from the human GH molecule (35).

One of the authors (ADR) (36) prepared and sequenced cyanogen bromide fragments from bovine GH that were tested in multiple bioassays [summarized in (33)]. None had more than weak activity. Larger peptides from the human molecule strengthened the core hypothesis. Li (37) digested a homogeneous preparation of hGH with pepsin under mild conditions to an extent of almost 40 percent. Separation from the undigested material was done under non-reducing conditions. There were no differences in activities

between intact hGH and the pepsin-altered hormone (at multiple doses) in both the tibial growth plate assay and the pigeon crop sac assay (for lactogenic activity). Taken together with data from partial chymotrypsin and carboxypeptidase digests, it is apparent that the activities of human pituitary growth hormone do not depend on the integrity of the entire molecule. One may *infer* that the activity resides in only a portion of the molecule. That does not mean that the core is *contiguous* because of the two disulfide bonds. Given that this was at a time when there was no evidence for an *independent* pituitary lactogenic factor, Professor Li concluded that it appeared that hGH possesses, as an intrinsic property, all of the biological effects characteristic of animal lactogenic hormones (37).

SOMATOMEDIN HYPOTHESIS AND IGF-1

Following the successful development of an immunoassay by Yalow and Berson to measure the concentration of insulin in plasma (38), a similar assay to measure growth hormone was validated soon thereafter (39, 40) and allowed the confirmation of the clinical diagnosis of growth hormone deficiency or over production.

Subsequently, there was steady progression (41) of development initially of bioassays for Somatomedin C (now known as IGF-I) then radioimmunoassay techniques for growth hormone and IGF-l (16).

The classic studies of Salmon and Daughaday (42) in the 19*50's* began a successful journey to understand the biology of growth hormone and the complex nature of its physiology. In their studies, these investigators demonstrated the need for production of a growth hormone-dependent factor to permit the growth promoting activity of GH. They showed that radiolabeled sulfate (SO4) could be taken up by rat cartilage, but that this process was diminished in hypophysectomized rats and not improved by placing GH into the *in vitro* system. However, serum from normal rats or from hypophysectomized rats treated with GH normalized the sulfate uptake (thus, the name "sulfation factor"). Over time, this factor(s) was isolated and had its amino acid sequence determined. The material had insulin-like activity, but blocked *in vitro* by an insulin antibody (thus, non-suppressible insulin-like activity, or NSILA). Finally, the growth promoting activity largely (though not completely) regulated by GH was clarified and two peptides were designated as being insulin-like growth factors (IGF-I and II) (43–45). Green and colleagues proposed a modification to the original hypothesis, denoting a "dual effector" theory of growth hormone action (46). The hypothesis indicated individual functions for GH and IGF-1 (somatomedin). The former promotes the differentiation of precursor, for example, cartilage cells and the latter leads to clonal expansion. Thus, the original endocrine hypothesis has become one of paracrine/autocrine action. The substantial complexity of this GH-IGF system continues to be assessed.

GROWTH HORMONE TREATMENT IN THE HUMAN

Human growth hormone was finally purified, noted to be separate from human prolactin, although there are some overlapping activities of these similar molecules and employed therapeutically to treat GH deficient children (24, 47–49). In a remarkable 60 y follow-up one of Raben's original patients was re-evaluated at age 78 y. He received hGH (Raben preparation) in 1956 at age 17 y at which time he was 129.5 cm, had no sexual development and a bone age of 7 yr. Two and one half years of hGH led to an adult height of 168.9 cm or 15.5 cm/y during those 21/2 y (50). He was subsequently treated with thyroid hormone, cortisone acetate, and testosterone. Spermatogenesis with successful conception was induced with hCG and human menopausal gonadotropins. MRI examination of the brain at 78 y revealed a tiny pituitary with absent infundibulum. Combined pituitary deficiency genetic panel did not reveal any clinically relevant variant and serum levels of GH, FSH, LH, and testosterone were undetectable (50). In addition in a tantalizing short paragraph titled: Treatment of adult hypopituitarism Raben noted that an adult woman with hypopituitarism had been fully treated with the agents available at that time-thyroid, ACTH and estrogen, but was not completely "well". Upon addition of growth hormone "…she noted increased vigor, ambition and sense of well-being" (51). Raben goes on to conservatively speculate, "Observations will be needed in more cases to indicate whether the favorable effect was more than coincidental" (51). In our opinion this is an "Ah Ha" moment for hGH to be effective in the hypopituitary adult and intentionally led to the trials of growth hormone in the adult for a number of purposes the non-GH deficient child, and doping in sport—brought to fruition with the production of recombinant hGH (rhGH).

The effects of growth hormone on growth and metabolism were shown in a group of 75 hypopituitary children by Wright and colleagues (52). They emphasized some metabolic aspects of the hormone in the short term and tried to correlate them to the change in height velocity in the longer term. This was not a new concept since others had previously noted the effects of hGH on metabolism, positive nitrogen balance, mineral retention and glucose intolerance (49, 53, 54). hGH administered to fasting subjects led to a fall in free fatty acids, glucose, α-amino nitrogen within an hour followed by a rise in FFA (54).

ROLE OF THE NATIONAL PITUITARY AGENCY

By the mid-1960s it was clear that human growth hormone was effective in GH-deficient children and especially helpful for those very young infants with hypoglycemia. This situation led to competition for human pituitary glands obtained at autopsy. To maximize gland collection, the distribution of hGH for clinical investigation and therapy, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) of the National Institutes of Health (NIH) and the College of American Pathologists formed the National Pituitary Agency, NPA (since re-named National Hormone and Pituitary Program, NHPP) which became responsible for all pituitary hormone-related therapy and many reagents for clinical and basic science research (55). A similar program was begun in Canada by the Canadian Medical Research Council.

The NPA was organized under the direction of Dr. Robert Blizzard along with others, Drs. Alfred Wilhelmi, Al Alberts, and several from the NIH (NIAMDD) with the purpose to coordinate the collection of human pituitaries, the extraction and distribution of hGH in a logical and sensible manner for both research and treatment. After a few years of private funding, the NIH provided for the NPA beginning in 1963. The methods for extraction and purification changed during the hGH program with "clinical grade" hormone moving from 1 to 3 IU/mg (essentially pure 22 kD monomeric hGH) (56). Until 1985 when the first few cases of Creutzfeldt-Jakob disease were discovered virtually all of the hGH distributed in the US came from this program. All patients under treatment were part of various research studies for at least the first part of their treatment program which was often interrupted since there was not enough hormone for all patients for each year. One learned a lot about catch-up and catch-down growth in those with hypopituitarism because of this problem (52). It is purported that human pituitary growth hormone added 17.7 km (~11 miles) to the heights of growth hormone deficient children in the US during the NPA distribution period (Blizzard, RM, personal communication).

SUMMARY (PRE-RECOMBINANT ERA)

The activity of growth hormone in humans has been known since at least Biblical times and then through the centuries with many giants/those with acromegaly noted in paintings (e.g., Goya's *Colossus*). It was not until the late 19th century that acromegaly was considered due to a pituitary tumor. A number of animal experiments were performed in the early 20th century that unequivocally noted a growth promoting hormone from the anterior pituitary, with growth hormone finally purified from the human in the late 1940s. Animal growth hormones were not active in the human (unlike insulin) and the first report of an adolescent with growth hormone deficiency treated with human growth hormone was noted in 1958. Growth hormone was in short supply until the recombinant era when clinical research efforts were expanded to many other conditions for which short stature was a sign in children/adolescent and abnormal body composition and diminished quality of life were signs and symptoms in adults with growth hormone deficiency.

RECOMBINANT DNA ERA

The story of the development and use of recombinant human GH (rhGH) is one of good fortune. Prior to 1982, peptide hormone therapy was relegated to the processing of animal or human cadaveric glands to extract, purify, and subsequently administer therapies such as insulin. As noted previously, because of species specificity of GH, only simian or human GH are metabolically effective in man. Pituitary hGH was used experimentally, but sparingly because of low supply, for many conditions that resulted in short stature. It showed much promise until several reports of Creutzfeldt-Jakob disease (CJD) emerged in 1985.

The description of the dramatic story of the occurrence, clinical presentation and ultimate demise of the index case of GH-associated CJD was told in clear and moving prose by the involved pediatric endocrinologist (57) ten years after the diagnosis. Within 6 months of presenting with ataxia, he had died. An autopsy concluded that he had had CJD (57, 58). Soon thereafter, Drs. Blizzard and MacGillivray described two similar cases (59). Many more followed (60) in the US and throughout the world, especially in France (61, 62). Distribution of pituitary-derived-GH (cadaveric) was swiftly halted in the United States and most of Europe in 1985 because of concern about a causal relationship with CJD, a fatal spongiform encephalopathy that had been previously reported to be capable of iatrogenic transmission through human tissue. To date more than 250 young adults who had received human cadaveric pituitary products have been identified with CJD with the sad likelihood that all affected patients will die of the disease. In the US, the onset of CJD is 14 to 33 years after starting cadaveric GH, while the large cohort of French patients had a median incubation of approximately 5 years less.

Vigilant NIDDK surveillance for this dreadful complication continues, although the incubation period would now be as long 40 years and hopefully at its conclusion [https://www.niddk.nih.gov/health-information/endocrine-diseases/national-hormone-pituitary-program/comprehensive-report]. An alternative treatment was clearly needed. This led to the whole saga of biosynthetic GH and the revolution in treatment of children and adults with rhGH.

Almost by design, recombinant DNA technology for GH developed at the same time that pituitary GH was being extracted and supplied by the NPA, as discussed in the previous section. In 1972, the first study demonstrating the use of recombinant DNA technology was published (63). By 1979, messenger RNA procured from pituitary tumors was used to reverse transcribe the hGH gene, which was subsequently inserted into the genome of *E. coli*. Two collaborating groups reported that these transfections resulted in production of GH protein that was biologically active in man (64–66). Once it was shown that GH could be produced safely and in mass quantities, the age of rhGH therapy began. Here, we review the history of the currently FDA-approved uses of rhGH in children and adults and *focus* on those studies that were pivotal to specific indications, some published after the FDA approval, but whose data were used in the decision to approve.

GROWTH HORMONE DEFICIENCY (1985)

The first product was methionyl growth hormone for at the time it was easier to produce and purify a form of the hormone with an additional methionyl group at the amino terminus of the molecule. Although the data for approval first appeared in the FDA submission file, many were published in the results of a clinical trial in 1986 (67). The results showed that the product was as biopotent as the pituitary formulation to promote linear

growth. It had the same metabolic effects (reducing blood urea nitrogen, increasing the serum phosphorous and alkaline phosphatase and raising the concentration of somatomedin C (IGF-1) (67). It had no more diabetogenic activity that pituitary hGH (67). After approval for pediatric GH deficiency studies were undertaken in many other forms of childhood short stature. Subsequent FDA approvals (pediatric) were noted for some (see below). Other conditions which included short stature were subjected to clinical trials, but did not achieve FDA approval. A few of the more prominent are outlined below.

CHRONIC RENAL INSUFFICIENCY (1993)

Although hGH had been used experimentally to treat patients with various conditions that included short stature prior to 1985, the advent of rhGH allowed for larger case series and formalized studies to determine in which conditions children may actually benefit from use. Starting in the 1970's, several groups started to posit the etiology of growth faltering in children with chronic renal disease, for some of the children are particularly prone to develop severe growth slowing and short stature. Inadequate nutrition may play a role, but there were hints that low somatomedin C (IGF-1) activity could also be an important contributing factor (68, 69). By the end of the decade children were undergoing GH stimulation tests that suggested that GH deficiency was likely not the cause of their slow growth, but rather GH resistance may be the underlying factor (70). Could "flooding the system" with rhGH be the answer to permitting children with CRI to grow more quickly?

Case series demonstrating rhGH administration to children with CRI would continue to be published through the 1980's, but it would be the 1990's that would finally bring published clinical trials that suggested that rhGH may be effective in increasing growth in this population. Hoekken-Kolega and colleagues performed a placebo-controlled, cross-over study in 16 children with CRI. Height velocity increased significantly when the patients received rhGH when compared to placebo. Although they were not followed to adulthood, it was concluded that adult height would likely be increased as well, since the bone age was not accelerated by treatment (71). The Kabi Pharmacia study group in Europe (KIGS) made similar conclusions after observational data were obtained from study participants demonstrating significantly increased height velocity after 2 years of rhGH treatment (the rate decreased in the second year, but was still above baseline) (72, 73). By 1993, the data were strong enough that rhGH was approved by the FDA for use in short children with CRI. Additional data have continued to emerge since approval and a consensus statement supporting the use of rhGH in this population has since been published (74).

TURNER SYNDROME (1996)

Henry Turner first described 7 women with "infantilism," webbed neck, and cubitus valgus in 1938 (75). As a condition that was universally accompanied by short stature, what became known as Turner syndrome was an appropriate candidate for a trial of rhGH therapy. Tanner and his colleagues described the use of pituitary hGH in 6 girls with Turner syndrome in 1971. Treatment was given for only a short time, but seemed promising as growth accelerated while receiving hGH (76). Six patients would be inadequate to advocate the use of hGH in all girls with Turner syndrome. But the stage had been set for others to perform clinical trials to increase height in these girls. In 1979, the Medical Research Counsel Working Party, established in Great Britain to study hGH use in children, did not find any growth response in 9 treated girls with Turner syndrome (77). Rudman and colleagues demonstrated an increase in height velocity when hGH was combined with oxandrolone (78). In 1982, a study including 2 girls with Turner syndrome showed accelerated growth when treated with a combination of hGH and androgen (fluoxymesterone) therapy (79). Despite the conflicting data, by 1983, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the American Academy Pediatrics were able to state that, "Preliminary data suggest the possibility that such patients [those with Turner syndrome] might benefit from hGH in combination with anabolic steroid therapy or even from rhGH alone," (80). It was time to turn preliminary data into more formal trials.

The end of the 1980's brought several clinical trials comparing different hGH regimens. Given previous data that suggested that growth increased when rhGH was administered along with androgens, these larger studies sought to determine if the addition of oxandrolone may increase growth over that induced by rhGH alone. Genentech, as the pioneer of rhGH production, sponsored a study of 70 girls with Turner syndrome randomized to receive their version of rhGH at the time (somatrem, methionyl GH), oxandrolone alone, somatrem plus oxandrolone, or no treatment. The group that received rhGH and sex steroid replacement grew most over the 2 year study period, followed by the oxandrolone group, GH group, and finally, those who had no treatment (81). Later studies tried to determine if adding estradiol to mimic the growth effect of pubertal maturation may have a synergistic effect on the hGH-induced growth response in Turner syndrome. In the short term, addition of estradiol in these studies had a minimal effect on growth when compared to using rhGH alone (82, 83).

But what about adult height? Small short term gains in height velocity were of little use if the women who received treatment would not gain some adult stature. Many of the groups that published data about the short-term effects found with rhGH also followed their patients to near adult height. Height gains between groups were variable as different dosing regimens and sex steroids were used, but adult height increased by 2-8.5 cm over initial predicted adult height when rhGH was administered along with either oxandrolone or ethinyl estradiol (84–88). Treatment also appeared to be safe (89, 90). Finally, the LWPES could state that there were enough data to advocate prescription of rhGH for girls with Turner syndrome (80). FDA approval would soon follow in 1996 (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) with follow-up studies corroborating an increase in adult height and normal body

proportions when GH was started prior to pubertal induction with or without oxandrolone therapy (91–94).

PRADER-WILLI SYNDROME (2000)

The first patients of what would later be termed Prader-Willi syndrome (PWS) (OMIM# 176270) were reported in 1956. An article appeared in German describing "A syndrome of obesity, short stature, cryptorchidism, and idiocy in children and adults who presented a myotonia-like picture as newborns" (95). The issue of short stature in this population would not be addressed again for more than 30 years. A preliminary report on the use of pituitary hGH in 4 children with PWS was published in 1987 by Lee and colleagues. They demonstrated an initial increase in height that slowed when hGH was stopped due to the concern of Creutzfeldt-Jakob disease (96). A follow-up report in 2 of the 4 children was published after the children were treated with rhGH and resumed their accelerated growth (97). These studies led to larger trials of rhGH administered for growth promotion in children and adolescents with PWS.

Children with PWS have many features consistent with GH deficiency, including short stature and sub-normal growth, increased truncal fat, and low IGF-1 concentration (98). These findings led to additional studies exploring whether the children actually have GHD (99). Data have demonstrated that children with PWS have hypothalamic dysfunction, including increased risks for ACTH and TSH deficiencies (100). In general, children with PWS have low GH production, as has been determined in subjects with obesity. Levels of IGF-I may be low in children with PWS, however, this contrasts to obese individuals who usually have normal levels and grow normally. Not all children with PWS have altered GH secretion (98) and adult GHD is quite uncommon in the PWS population (101). The reasons for short stature and subsequent positive growth response to rhGH in PWS remain elusive.

Although children with PWS were initially included in studies regarding use of rhGH for short stature, observations began to emerge that suggested that rhGH could increase lean body mass and decrease fat mass (102, 103). This is especially important given the severe obesity that often accompanied a diagnosis of PWS. Larger controlled studies corroborated what was found in the earlier observational studies (104–106). Although published after FDA approval, there have been more recent suggestions that rhGH may improve cognition in children with PWS, if started at a very young age (107–109), although this continues to be debated. In 2000, the FDA had enough information to approve the use of rhGH for children with PWS.

Concerns about rhGH therapy and its relation to adverse outcomes in children with PWS started to emerge within a few years of FDA approval. In Europe, a 6 year old boy with PWS treated with rhGH died suddenly. He had a longstanding history of respiratory pathologies including CPAP-dependence in the neonatal ICU, repeated atelectasis, and pneumonia. However, he developed episodes of sleep apnea only after initiation of rhGH therapy (110). That PWS had been associated with respiratory problems made it difficult to determine a causal relationship between the rhGH treatment and the sudden death in this patient. Additional deaths of patients with PWS in the months following initiation of rhGH continued to emerge (111–113). In 2006, the Pfizer International Growth Database (KIGS) reported 5 children who died suddenly amongst 675 patients with PWS. All died of respiratory disease (114). A trial examining polysomnograms in children with PWS treated with rhGH did not show any increase in obstructive events. However, 1 child, who had had a normal polysomnogram both prior to and after starting GH treatment did die during the trial during a mild respiratory illness (115). The data continue to be conflicting whether sudden death in PWS is inherent to the disease itself or is exacerbated by rhGH treatment. Current rhGH labeling mentions the risk of sudden death in rhGH-treated children with PWS.

SMALL FOR GESTATIONAL AGE WITHOUT CATCH-UP TO NORMAL STATURE (2001)

Although many children may have short stature, but be born with normal length, certain children start life small and never catch up. The term small- for-gestational age (SGA) has been used to describe those children born smaller than expected. The definition has varied among medical disciplines, but the endocrine community has considered SGA to describe those children born below 2 standard deviations for gestational age and sex for length, weight, or head circumference (116). Children born SGA constitute a heterogeneous group, some have no known underlying medical condition (117). This has made studies of treatment with rhGH in children born SGA with inadequate catch-up growth difficult. Additionally, what constitutes "catch-up" has varied. In the US, the FDA has not defined a minimum height SDS below which rhGH should be considered in SGA children. However, it is generally assumed that patients who do not achieve a length or height that is on the appropriate growth chart for age and sex may be considered for rhGH treatment. In Europe, the criteria are stricter; only children born SGA who remain more than 2.5 SD below the mean for age and sex, who have below average height velocity, and a height SDS more than 1 SD below mid-parental height SDS at age 4 may qualify for rhGH treatment (116). Nevertheless, as a group that had potential to benefit from rhGH therapy, studies were done relatively soon after the use of pituitary hGH showed accelerated linear growth in several SGA subpopulations.

Children with Russell-Silver syndrome are universally born SGA (118–120). In 1969, Tanner and Ham treated 2 children with Russell-Silver syndrome with hGH. Their growth increased, providing a proof of concept that hGH may work, at least in this rare condition (Tanner and Ham, 1969 (121). In the 1970's, several studies examined hGH treatment in children born SGA who failed to catch up to the normal growth curves including some without a known cause for their small birth size. The response to GH was very variable, with some children increasing

in growth similar to those with mild GH deficiency, although others had little to no response (122–124).

It would take until the mid-1990's for large, multicenter studies to publish data regarding rhGH effects in children born SGA and who failed to catch-up to the normal growth curves. Several studies demonstrated increase in growth and higher predicted or near adult heights in prepubertal children born SGA treated with rhGH (125, 126). Higher doses were needed to achieve increased height velocity as compared to children with GH deficiency (127). In fact, growth occurs in the SGA group in a dose-dependent fashion, with higher doses inducing additional catch-up growth compared to lower doses (128, 129). With the added potential benefit of decreased fat and increased muscle mass (130, 131), the FDA approved the use of GH in children born SGA with inadequate catch-up growth in 2001.

IDIOPATHIC SHORT STATURE (2003)

Of all the indications for rhGH, ISS is likely the one that has garnered the most debate within the endocrine community. It has brought to the fore such questions as, "Is short stature a disability," "Is the goal to attain normal height or maximal height," and, "What exactly are we treating" (132, 133)? Nevertheless, due to the large number of studies that have demonstrated the growth-promoting effect of GH in non-GHD children, the FDA did approve the use of GH in children with ISS is 2003.

In 1984, the first case series attempting to demonstrate a positive effect of hGH in children with ISS was published (134), although there were a number of children who likely had ISS who had been previously treated with hGH in other studies (76). In a study by Grunt and colleagues, seven children with no specific reason for diminished growth were treated with hGH. Five of these patients had an increase in height velocity with a subsequent slowdown after hGH was discontinued (134). This small proof-of-concept study paved the way for pharmaceutical companies, several of which started producing rhGH in the 1980's after the success of Genentech, to sponsor larger studies to evaluate if children with ISS may benefit from rhGH administration. As expected, the results of the many trials performed from 1989 through the 1990's demonstrated variable growth results, but the overarching conclusion was that most children with ISS did have an increase in height velocity and (near) adult height when treated with rhGH. This was later corroborated with a meta-analysis performed in 2002. This study evaluated 38 previous reports and concluded that rhGH administration resulted in a 4-6 cm increase over predicted adult height in heterogeneous groups of children with ISS. It was also predicted that the cost per centimeter of treating children with ISS was approximately $US14000, fueling the debates that remain today regarding rhGH administration in this cohort (135).

Why should children with no underlying hormone deficiency respond to rhGH? This, of course, had been asked of other conditions such as Turner Syndrome and children born SGA with inadequate catch-up growth. However, the ISS group has fascinated many since outside of short stature, these children apparently have no other discernable medical issues. In the 1980's several studies sought to determine the cause or causes of ISS. The first attempts evaluated whether hGH secretion was altered in any way. Several studies, using different methods of GH stimulation and spanning into the 1990's, were not able show that GH secretion was disrupted in any way in those with ISS (136–138). Later, groups suggested that changes to GH binding protein concentration (139, 140) or function (141, 142) might result in mild GH resistance and accompanying short stature.

The difficulty in studying children with ISS has always been that the cohorts studied are heterogeneous and as time goes on, what constitutes "idiopathic" changes, especially as whole exome and genome sequence determinations become more available. Nevertheless, ISS remains in itself, a common reason for rhGH administration. Because of the controversies regarding treatment of children with ISS with rhGH, the necessity of attempting long-term follow-up for safety monitoring is apparent.

The growth plate itself has become of interest in attempts to disentangle the broad category of ISS. Natriuretic peptide receptor type B, encoded by the *NPR2* gene is intimately involved in the complex regulation of growth. The endogenous ligand is the C-type natriuretic peptide. The prevalence of *NPR2* variants in those with familial short stature (a variety of ISS) was noted as approximately five percent (143).Therapeutic trials with rhGH show increases in C-type natriuretic peptide and its amino terminal pro-peptide (NTproCNP) (143) and accelerated growth (144).

SHORT STATURE HOMEOBOX-CONTAINING GENE DEFICIENCY HAPLOINSUFFICIENCY (2006)

This indication for rhGH is a perfect example of a condition that was identified and removed from the category "idiopathic" short stature. In fact, in the early 2000's, several studies demonstrated that SHOX deletions were a relatively common underlying cause for ISS, approximately 2 to 3 percent, although this may be above 10% in selected clinical populations (145, 146). The short stature homeobox-containing gene (SHOX) was first sequenced and suggested as a cause of short stature in girls with Turner syndrome and some children with ISS in 1997 (147). To test the hypothesis of whether children with SHOX haploinsufficiency would respond to rhGH as those with Turner syndrome would, 2 children were treated with rhGH at Turner syndrome doses in 2000. Their growth over 1 year of treatment increased significantly. In fact, over that 1 year, the amount of height gained (+0.9 and +1 SD, respectively) was greater than the mean response in those with Turner syndrome (+0.55SD) (148).

Interestingly, after the association between SHOX haploinsufficiency and Turner syndrome was established, it did not take very long for the FDA to approve rhGH treatment for those children with SHOX deficiency. In fact, the first randomized, controlled trial to be performed using rhGH in children with SHOX haploinsufficiency was not published until 2007, one year *after* FDA approval (149). Since that time, follow-

up data have shown that children with SHOX haploinsufficiency started on treatment with rhGH in the prepubertal period can have a height gain of 1.2 SDS (approximately 8 cm) by the time they reach near-adult height (150).

NOONAN SYNDROME (2007)

Noonan syndrome is the most recent FDA-approved indication for use of rhGH in children. Jacqueline Noonan first reported on 19 children with similar features including pulmonary stenosis, ptosis, low-set ears, and short stature in 1968 (151). As with Turner syndrome, it was noted over time that children with Noonan syndrome usually had short adult stature and diminished childhood growth (152, 153). As a result, they were prime candidates for an attempt at rhGH treatment. The first report of rhGH treatment in 3 children with Noonan syndrome did not find any increase in height (154). However, several case series in the 1990's suggested that some patients may benefit from rhGH treatment (155, 156).

In 1996, a large study examining the effect of rhGH in children with Noonan syndrome over 4 years of treatment demonstrated that in most, growth increased, although less than in a group of children with hGH deficiency (157). It wouldn't be until the next decade that Noonan syndrome was found to be heterogeneous and caused by several genes that resulted in variable phenotypes. Although children with Noonan syndrome had increased growth when receiving rhGH in general, those with the *PTPN11* mutation had the most severe phenotype and responded the least to treatment (158–160).

Before rhGH could be approved for children with the Noonan syndrome, it had to be shown that not only was treatment effective, but it also had to be safe. Given the risk of hypertrophic cardiomyopathy in this population, concerns arose that rhGH may worsen this potentially life-threatening condition. In 1996, a group of 30 patients with Noonan syndrome were treated with rhGH, but did not develop cardiomyopathy. However, this was an observational study without a control group. Additionally, those with pre-existing cardiomyopathy were excluded, not allowing for an examination of whether rhGH worsened this condition (161). In 2001, this missing piece was examined in a study comparing children with Noonan syndrome with underlying heart disease to those who did not. The study group was small and not all had hypertrophic cardiomyopathy, but it was performed over 3 years and did not show any worsening or development of heart disease (162). In 2007, the FDA had enough information to approve the use of GH in children with Noonan syndrome.

A subsequent review of the efficacy and safety of rhGH in Noonan syndrome was performed by Dr. Noonan herself. The review demonstrated an increased height velocity in the first year of treatment and an average near adult height gain of 0.6-1.7 SD when using standardized Noonan syndrome growth curves. Earlier initiation of treatment as well as earlier pubertal status when starting rhGH both seem to be associated with taller near adult height. rhGH appears to be safe in children with Noonan syndrome. The available data reviewed did not demonstrate any exacerbation of cardiac pathology, worsening of glucose metabolism, and no increased risk for cancer. It should be noted, however, that patient numbers in the safety studies reviewed were small necessitating continued monitoring of children with Noonan syndrome who are treated with rhGH (163).

SOME OTHER CONDITIONS FOR WHICH RHGH HAS BEEN STUDIED, BUT DO NOT HAVE FDA APPROVAL

Endocrinologists have considered hGH for a variety of children with many conditions for which short stature is a prominent finding. Before the advent of rhGH the supply of hGH was often the limiting factor; however, there were some data to indicate accelerated growth in children with Turner syndrome and small-for-gestational age in a small number of subjects (for example, see Tanner (76, 164). With the supply issue largely moot after the release of rhGH children with multiple other conditions were subjects in trials with rhGH. We have chosen to review data for those with cystic fibrosis, X-linked hypophosphatemia, and achondroplasia (which does have an indication in Japan).

For two other conditions, juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD), mainly Crohn's disease, significant numbers of children have been treated with rhGH. Both are complex conditions for which marked inflammation (JIA) or inflammation, infection and malabsorption of food (Crohn's disease) are prevalent. The children with both conditions may be at many stages of their disease process with multiple non-pharmaceutical interventions (e.g., dietary) as well as multiple anti-inflammatory and antibiotic medications, and surgery. Most children receive pharmacological amounts of glucocorticoids. Thus it may be difficult to disentangle the specific effect of rhGH from the myriad other interventions in these complex patients.

Perhaps more narrowly crafted trials might be better suited to test the effects of rhGH (or IGF-1, as some have noted resistance to the effects of rhGH). One might consider, for example, a prospective study with 3 matched study groups of prepubertal children with Crohn's disease: one with an anti-inflammatory alone (for example, infliximab, anti-TGF-β); anti-inflammatory + rhGH (or rhIGF-1); and the growth factor alone.

Given these constraints and the lack of truly evaluable studies, we have chosen not to summarize them. Although the same may be said about children with cystic fibrosis, the therapy for them is more standardized (non-pharmaceutical as well as antibiotics and pancreatic enzyme replacement). We have chosen to summarize them.

Cystic Fibrosis (MIM #602421)

Growth in children with cystic fibrosis (CF) has become much more robust and virtually physiologic over the past 5 to 6 decades. Data reported in 1975 noted body weights mostly between -1.0 and -2.0 SD compared to the normal weight curves, but with a sharp descent above age 10 y (165). The

data were obtained when the majority of children did not survive into the second decade. Data from Toronto, which had a superb clinic for children with cystic fibrosis, showed that 6% of boys and 12.5% of girls ≥ 8 y were below the 3rd centile for height and 37% of the boys and 40% of the girls were above the 50th centile for height. For weight 8% of the boys and 16% of the girls were below the 3rd centile and 41% of boys and 26% of girls were above the 50th centile. Relevant factors include at first non-pharmaceutical such as physical therapy and nutritional replacement, both macro- and micro-nutrients. Important pharmaceutical agents include anti-bacterial agents, DNAase, pancreatic enzyme formulations, and much more recently the "correctors" such as lumacaftor or tezacaftor and "potentiators" such as ivacaftor (166). These "correctors" and "potentiators" affect the cystic fibrosis transmembrane conductance regulator (CFTR), an ATP-gated anion channel, mutated in those with cystic fibrosis. In the ensuing years the height and weight deficits (compared to physiological growth) have diminished, although most studies report greater catch-up for weight than for height.

Stalvey and co-workers (167) assessed linear growth and weight in 83 children with cystic fibrosis, 6 to 11 y, enrolled in two clinical trials, the longitudinal, observational GOAL study and the placebo-controlled ENVISION study to evaluate the effects of ivacaftor, a CFTR potentiator. Height and weight Z-scores increased over 6 mo (GOAL); height and weight Z-scores increased over 48 weeks (ENVISION) and were greater in the ivacaftor group than in the placebo group—height 7.08 *versus* 5.99 cm; weight 6.45 *versus* 3.34 kg. However the change in the weight Z-score (0.36) was greater than the change in height Z-score (0.17) with the attained weight still at higher Z-score than the height (0.44 *versus* 0.17).

We shall move to clinical trials with rhGH (~0.3/mg/kg/wk) *versus* either an observational group or one with this standard dose *versus* a higher dose (~0.5 mg/kg/wk) group. There were a relatively small number of trials with rhGH. These studies, which are detailed in the Cochrane Library Database of Systemic Reviews (168) are briefly summarized for some pulmonary function, auxologic and blood glucose outcomes, below. Subjects, 291 in total, ages 5 to 23 years were evaluated in 8 clinical trials, all but one at the standard dose of 0.3 mg/kg/wk. The trials were for ~1 year with several for ~6 months. Most of the trial data were limited by low quality of evidence, inconsistency across trials, small numbers of subjects and short duration when considering the entire growth period. The results noted increased height velocity in the intermediate term, but none were taken to (near) adult height.

For those studies for height (n=156) and weight (n=62) and of ~1 y duration the mean HV in the rhGH group was 3.53 cm/y *greater* which attained statistical significance in favor of the interventional group. For weight, the intervention group was 1.0 kg heavier at the end. When the higher dose of rhGH was compared to the placebo the former grew on average 3.3 cm/y more (CI 1.17-5.43 cm). That difference achieved statistical significance. Although the weight gain was 0.80 (CI -0.44 to +2.0 kg) more in the rhGH group, the difference did not achieve statistical significance. These intermediate term data *versus* no treatment showed increases in height and weight, but without a dose response when considering the standard dose *versus* the higher dose. Virtually all showed a small rise in fasting blood glucose levels that were neither statistically nor clinically significant. No subject met the criteria for CFRD or Type II diabetes.

The primary pulmonary outcomes showed no or small changes in FEV_1 (% predicted) compared to no therapy or with the standard dose compared to the higher dose. Also included are other issues such as pulmonary infections and pulmonary exacerbations and quality of life. All are extensively noted in the Cochrane Database (168).

Taken together these intermediate term data show relatively small changes in height velocity and height SDS as well as for weight. The pulmonary function tests did not increase toward normal but did not show the expected annual decrement of 2 to 3% (169) and there were minor increases in fasting blood glucose level. The level of the evidence was mainly weak using the Cochrane Library Database criteria. Many of the studies were done one and two decades ago when the non-pharmaceutical interventions were being optimized and children with CF were not as well grown as they are today, especially with the newer pharmaceutical interventions. We do not believe that there is a role for rhGH therapy in children and adolescents with CF, whether the end points are pulmonary, infections, metabolic or auxologic.

We believe that a randomized study with matched initial conditions using the best non-pharmaceutical interventions and optimal nutritional and physical therapy interventions as well as non-rhGH pharmaceutical agents such as vitamins, pancreatic enzymes, antibiotics and the "caftors" to test whether standard dose or high dose (perhaps 0.7 mg/kg/week) rhGH might accelerate linear growth and augment lean body mass. Careful consideration of carbohydrate metabolism would be important given the incidence of CFRD.

X-Linked Hypophosphatemia (MIM #307800)

X-linked hypophosphatemia (MIM #307800) is a rare skeletal dysplasia (prevalence ~1:25,000) featuring renal phosphate wasting and disproportionate short stature. Excessive amounts of fibroblast growth factor 23 (FGF-23) result in hypophosphatemia due to excessive renal phosphate excretion and inappropriately low levels (for the level of phosphate) of 1, 25 di-hydroxy vitamin D (1, 25 $[OH]_2$ D]. The result is a skeletal dysplasia (rickets) and growth faltering due in part to a primary defect in osteoblasts (170). Therapy for this condition has changed little over the past few decades, until the approval in 2018 of burosomab, a fully human monoclonal antibody against FGF-23 (171). The antibody is effective by binding to FGF-23 and inhibiting its signaling. It increases renal tubular reabsorption and gastrointestinal absorption of phosphate increasing the serum level of phosphorous and ultimately ameliorates rickets and increases bone mineralization.

To characterize growth faltering in children (n=228) with XLH Mao and colleagues (172) constructed cross-sectional

growth curves (for height) of affected children, the vast majority of whom received conventional supplemental therapy with phosphate and an active analog of vitamin D. The subjects were mainly those entered into clinical trials for burosomab and the data indicate their pre-trial stature. In summary, most are born at average length percentiles, but show diminished height velocity within the first year of life. Height velocity and height SDS progressively declined during early childhood and remained deficient thereafter. These data are quite compatible with those of Cagnoli and co-workers (170) who published curves of height for those children evaluated at their clinic, but before any therapy was prescribed.

Segmental growth was affected with leg length decreasing (relatively) progressively during childhood and adolescence. Sitting height, but especially the sitting height index (ratio of sitting height to stature) declined: at age 2 y it was +2 SD, but by age 10 y it had risen to +3.3 SD (173). These findings indicate uncoupled growth of the trunk and legs.

Seikaly and co-workers (174) performed a randomized clinical trial with cross over for rhGH, but in only 5 subjects with XLH. Over 12 months in the treatment group the height Z-score increased to -1.46 from -2.66 SD at the start; there was virtually no change in the control group -2.22 SD compared to -2.27 at the start. The height velocity changed remarkably in the treated group rising to +4.4 SD during rhGH treatment, but remained low (~-1.90 SD) during the control period.

Zivicnjak and colleagues (173) evaluated 16 pre-pubertal children with XLH receiving conventional phosphate and active vitamin D therapy during 3 years in a randomized open-label trial with rhGH administration. For comparison, the same follow-up evaluations were done in a "reference" population of 76 children with XLH receiving the same conventional therapy. At enrollment the children were significantly short (-3.3 SD, for height). Leg length was most impaired (-3.8 SD), and sitting height most preserved (-1.7 SD), yielding a markedly abnormal sitting height index (+3.3 SD). Over the three years of the study there were sustained increases in linear growth (stature, +1.1 SD); sitting height (+1.3 SD) and leg length (+1.3 SD). No significant differences were noted in the controls. These changes including a stable sitting height index remained proportionate in the treated children and controls; however, the sitting height index continued to further increase in the reference population. Eleven patients reached (near) adult height. Their height, sitting height, leg length, and arm length exceeded baseline values by 0.7, 1.7, 0.7, and 1.2 SDS, respectively. Only the sitting height differed significantly from the initial measurements (in SD units).

Other studies on small numbers of subjects have been completed, but not under RCT conditions.

Achondroplasia (MIM #100800)

Achondroplasia is a common skeletal dysplasia characterized by short stature, rhizomelic shortening of the limbs, trident hands, genu varum, excessive lumbar lordosis and relative macrocephaly. Its genetic basis is a gain of function mutation of the fibroblast growth factor receptor 3 (FGFR3). That permits unbridled proliferation of chondrocytes at the growth plate. The limbs are more affected than the trunk with adult height in the range of -6 to -7 SD compared to the general population. Natural history studies note progressive height deficit as the predominant growth pattern (175).

Once rhGH became available in large quantities children with achondroplasia were considered for therapy. In 1997 Japan became the only country whose medicines approval group (Pharmaceutical and Medical Device Agency) granted a license for use in those with achondroplasia. The first year height velocity was significantly increased over the baseline; however, the increments in the ensuing years were significantly less. Thus, short term growth was more physiologic with a sharp drop-off (**Table 1**). Similar to responses to rhGH in children with other (often mild) skeletal dysplasias, a super-physiological treatment dose led to greater growth.

The data are summarized succinctly in a meta-analysis (176). From the selected studies 558 rhGH treated children with achondroplasia were evaluated. The median dosage was 0.21 mg/kg/wk, mainly because most of the studies were done in Japan, where the usual dose of rhGH is closer to 0.16 mg/kg/wk. The baseline height was -5.1 SD that progressively increased during treatment (**Table 1**).

The mean height gain at 60 months, but evaluated only for 21 patients, was 1.1 SD. The height gain stabilized after 24 months.

The effects of rhGH on the disproportion between the limbs and trunk are largely unknown. The same meta-analysis noted above found only 2 studies in which sitting height was properly evaluated (177). It progressively increased over 24 months (n=50 children) from -1.5 SD (95% CI -2.4 to -0.58 SD) to -0.47 SD (95% CI -1.2 to +0.22).

Limb-lengthening surgery may sometimes be performed as well. The children noted in the above analysis (rhGH treatment) did not have such surgery at the time of the study. More recently C-type natriuretic peptide has been evaluated as a potent stimulus of endochondral ossification. Several studies with an analogue of C-type natriuretic peptide have been completed with current long term extensions (178, 179). With this growth promoting agent, children continued to show modest increases in height velocity at least up to 42 months (178) in contrast to the rapid fall in height velocity after the first year in the rhGH clinical trials.

LONG-ACTING GH

We have written about the uses of rhGH in children, adolescents, and adults with diagnoses ranging from GH deficiency to various conditions of faltering growth that are responsive to rhGH

TABLE 1 | Growth in children with achondroplasia treated with rhGH.

	number	Height (SDS)	95% CI
baseline	498	-5.1	-5.1 to -5.0
12 months	494	-4.3	-4.4 to -4.3
24 months	102	-4.1	-4.1 to - 4.0
60 months	21	-3.9	-4.7 to - 3.2

therapy. A difficult issue relating to rhGH treatment has been the challenge of requiring daily administration of the drug. Adherence to such treatment regimens can lead to large variations in the evaluation of efficacy in any one of the treatment programs that we have discussed above. Thus, the potential availability of long-acting GH (LAGH) preparations, if safe and effective, would be an advantage to overcome the difficulties of requiring daily injections. Two detailed reviews discussing LAGH data (177, 180) and a meta-analysis (181) comparing LAGH to daily treatment provide information about the various formulations that are becoming available. We will briefly describe a few of these.

Speaking generally, there are a number of considerations that require assessment of any one of the products. To achieve satisfactory prolonged duration of action, enabling the delivery of hGH at one, two, or four week intervals, a number of companies have designed new molecular entities that have favorable pharmacokinetic and pharmacodynamic properties. Lack of damage or inflammation at the injection site, slow and steady absorption of the injected material, and reproducible, passage of the modified hGH protein from circulation into GH action sites are requirements. Effective bioavailability with adequate generation of IGF-I is necessary, as well as increased height velocity, which at least mirrors that associated with daily rhGH treatment regimens.

Each preparation differs in its pharmacokinetics, pharmacodynamics, efficacy and safety profile as they are different molecular entities. This makes it difficult to determine when to obtain a level of IGF-1 following the injection to determine the average IGF-1 level as either a safety or efficacy indicator. With daily rhGH one can obtain a level almost any time of any day and be close to a steady state level to make decisions about titration for inadequate efficacy or possible safety issue. For the new, long-acting compounds, one must obtain the full weekly IGF-1 pattern, denote the time when it is close to the average and then one can mathematically determine when the peak is most likely to occur, as well as the average concentration. For example, Kildemoes and colleagues have discussed this consideration for Somapacitan (182).

The authors demonstrated that obtaining a sample for determination of the IGF-I level on day 4 gives an accurate estimate of the mean IGF-I level and determination of IGF-I on day 2 gives an accurate estimate of the of the peak IGF-I level.- The lowest point is usually just before the next weekly injection.

Depot Preparations

The first LAGH approved in the United States (Genentech; Nutropin Depot) was that of rhGH encapsulated in biodegradable (polylactide-coglycolid) polymer microspheres. There was moderate biological activity with catch-up growth, but some disadvantages of the release of a big burst of rhGH in the first few days following administration as well as sub-therapeutic concentration toward the end of the interval between injections. Troublesome local injection site reactions and issues with large scale production, however, led to discontinuation. In contrast, Declage (Eutropin Plus, Somatropin Biopartners) is produced with rhGH reconstituted in MCT oil and then the resultant hyaluronate microspheres are dissolved by tissue hyaluronidase. Efficacy and safety in non-inferior comparisons to daily rhGH (10.2 cm/y vs 11.1 cm/yr) have been demonstrated leading to approval for use in pediatric GHD for pediatric GHD in South Korea (183).

PEGylated Preparations

Different polyethylene glycols (PEG), which are biologically inert minimally immunogenic compounds, have been added to GH (PEGylated), among other proteins, to increase their circulatory half-life. Several of the early preparations had local injection site reactions, such as lipoatrophy, along with accumulation of PEG in the choroid plexus cells. These problems led to discontinuation of several products other than Jintrolong, which has been produced by GeneScience Pharmaceuticals (China). Jintrolong is a safe and efficacious drug administered once weekly. It is approved for the treatment of children and adolescents with GH deficiency. The large Phase III trial showed a robust increment in growth leading to approval for use in children with GHD in China (184).

Prodrug Preparations

TransCon GH (produced by Ascendis Pharma) is a sustained release, unmodified rhGH that is reversibly bound to a PEG carrier molecule *via* a "proprietary" linker. The rhGH is slowly released from this PEG carrier by cleavage of the linker that is temperature and pH dependent with renal excretion. Phase II studies have shown augmented linear growth velocity and increased IGF-I production comparable to that following daily rhGH administration (185). Phase III studies of TransCon GH are underway in young children with GHD and in older patients who had previously been treated with rhGH.

NON-COVALENT ALBUMIN BINDING GH

Somacpacitan (produced by Novo Nordisk) reversibly binds to albumin with an increased affinity because of a single amino acid change and thus has a prolonged half-life. Phase II studies showed good toleration of the drug in children who had been small for gestational age infants, along with children with GHD (186). Growth responses in those with GH deficiency are not inferior to those previously treated with daily rhGH. Phase III studies are now being pursued in children and adults with GH deficiency. Use in adults with GH deficiency showed reduced truncal fat and improved body composition which could lead to approval for use in adult GHD and thus, possibly, to off label use in childhood GHD.

GH Fusion Proteins

A number of proteins have been fused to rhGH to attempt to prolong action by increasing the half-life and delaying renal clearance. HyTropin (Produced by Genexine and Handok of South Korea) is fused to the Fc-domain of immunoglobulin. A Phase II study in Europe demonstrated efficacy and apparent safety in adults with GH deficiency (187).

Somatrogon (produced by OPKO and Pfizer) is a chimeric protein generated by fusing three copies of C-terminal residues of human chorionic gonadotropin beta subunit to the coding

sequence of rhGH. A robust growth response found in children treated with Somatrogon was similar to or greater than that seen in prepubertal children with GHD receiving daily rhGH (over 12 cm/yr in a Phase II study) (188). Phase III testing is underway.

CONCLUSION

These and presumably other LAGH preparations will become available for use in children, adolescents, and adults in whom hGH treatment is clinically indicated. All of the challenges of determining dosing, modes of administration, methods of monitoring clinical responsivity, and seeking ways of describing long-term safety and efficacy will be as necessary as with daily rhGH treatment. The potential availability of multiple LAGH preparations that could be used will make long-term scrutiny of these GH treatment programs even more difficult than with daily rhGH using basically the same treatments because each is a separate chemical entity and adds different excipients (180).

AUTHOR CONTRIBUTIONS

EG drafted and wrote major parts of the manuscript, and reviewed multiple drafts of the entire manuscript. ER drafted and wrote major parts of the manuscript, and reviewed multiple drafts of the entire manuscript. AR conceived the project and drafted and wrote major parts of the manuscript, and reviewed multiple drafts of the entire manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency

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The syndrome of impaired GH secretion (GH deficiency) in childhood and adolescence had been identified at the end of the 19th century. Its non-acquired variant (naGHD) is, at childhood onset, a rare syndrome of multiple etiologies, predominantly characterized by severe and permanent growth failure culminating in short stature. It is still difficult to diagnose GHD and, in particular, to ascertain impaired GH secretion in comparison to levels in normally-growing children. The debate on what constitutes an optimal diagnostic process continues. Treatment of the GH deficit *via* replacement with cadaveric pituitary human GH (pit-hGH) had first been demonstrated in 1958, and opened an era of therapeutic possibilities, albeit for a limited number of patients. In 1985, the era of recombinant hGH (r-hGH) began: unlimited supply meant that substantial long-term experience could be gained, with greater focus on efficacy, safety and costs. However, even today, the results of current treatment regimes indicate that there is still a substantial fraction of children who do not achieve adult height within the normal range. Renewed evaluation of height outcomes in childhood-onset naGHD is required for a better understanding of the underlying causes, whereby the role of various factors - diagnostics, treatment modalities, mode of treatment evaluation - during the important phases of child growth - infancy, childhood and puberty - are further explored.

Keywords: growth hormone deficiency (GHD), diagnosis, childhood, puberty, GH treatment, adult height

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INTRODUCTION

The fundamental findings relating to the chemical structure of pituitary growth hormone and its biological effects on growth and metabolism in various animals were described in the first half of the 20th century (1). The major driving forces in this field were Herbert Evans and his collaborators (2). By the beginning of the next half of the century, when the species specificity of primate GH in humans had been discovered and methods to purify GH from pituitaries of men and monkeys had been refined, the first studies to prove the efficacy of this peptide hormone were conducted. In 1958, human pituitary GH (pit-hGH) was shown to promote growth in a GH-deficient adolescent over a period of several months (3). Human and monkey pituitary GH revealed a variety of short term (days) metabolic effects in adolescents and adults with hypopituitary disorders (4). The era of pit-hGH ended in 1985, when hGH produced *via* recombinant technology became available. This

initiated the era of virtually unlimited availability of r-hGH worldwide and the expansion of its use in adults with GHD, in children with growth disorders and for other indications.

The primary aim of this article is to review the effect of GH treatment on growth, predominantly in children and adolescents with GHD and to evaluate our current understanding of the factors affecting the magnitude of the response in the short- and long-term. Such an evaluation not only requires a review of the specific literature pertaining to treated cohorts but also necessitates a discussion – from a historical perspective – of the instruments and their suitability in establishing the diagnosis of GHD, along with the tools used to analyze the growth response during different developmental phases.

CLASSIFICATION OF GROWTH HORMONE DEFICIENCY

By definition, GHD is a syndrome caused by the impaired secretion of GH. This can be the consequence of a disorder at the level of the pituitary itself and/or within the cascade of function and structures of the hypothalamus or brain which regulate its secretion. However, the wider understanding of the term GHD also includes disorders resulting from impaired action of GH at the cellular level. After recognizing that GH-dependent components of the IGF-family were involved in mediating the effects of GH, the concept was nurtured that IGF was at the center of a GH–IGF regulatory system (5). On the basis on this concept, a distinction between *secondary* IGF-deficiency [IGFD] (as in GHD) and *primary* IGFD (=non-GHD) was proposed (6, 7).

Although this was a logical approach and suited for the clinical sub-classification of the GHD syndrome, it was simplistic and did not do justice to the complexity of the IGF-system (5–14). The major peptides of the IGF system in blood - IGF-I, IGFBP-3 and ALS - are GH-dependent and their levels in blood are quantitatively related to the GH secreted (15). But their levels in blood are also dependent on many other factors, for instance, hormonal or nutritional status (16, 17). In addition, growth promotion at the cellular level of the epiphyseal growth plate requires the local presence of both IGF and GH, whose quantitative relationship with their circulating levels is not fully understood (11, 12).

From the clinical perspective, it needs to be understood that GHD is also classified according to descriptive characteristics rather than a uniform principle (7). Some examples are:

- the onset of its origin: congenital/non-acquired *vs*. acquired;
- the hormonal extent of a pituitary defect: isolated (GH deficiency only) *vs*. combined [with other pituitary hormone deficits];
- the known cause: causal [specific cause known] *vs*. idiopathic [cause unknown];
- the extent of GH impairment: complete *vs*. incomplete (partial);
- its existence over the lifespan: permanent *vs*. transient;
- the age of disease discovery: during infancy, childhood, adolescence, or adult life.

PREVALENCE – INCIDENCE OF GHD

Reports on the incidence or prevalence of GHD in children are scarce. In the pit-hGH era, when very short children (height < -3 SDS) used to be diagnosed and a GH cut-off to tests of < 5 ng/mL was applied, an incidence of 1:4000 and a prevalence of 1:5,000-30,000 were reported (18–20). During the r-hGH era, when the test cut-off was at 10 ng/ml, an incidence of 1:3,400 and a prevalence of 1:29,000 were reported (21). After r-hGH became available in 1987, a doubling of the incidence in childhood-onset GHD in Denmark was observed, which was similar to that in southern Germany (22, 23).

DIAGNOSING GHD IN CHILDREN AND ADOLESCENTS

There is no single tool to confirm GHD. Thus, the diagnosis must be established by means of a variety of symptoms, signs and test results. The interpretation of non-clinical investigations must always be in accordance with clinical findings. Quantitative results need to be based on methodologically correct procedures and must be compared with appropriate normative references. Abnormal test results should always be repeated, particularly if they do not correspond with other findings.

The diagnostic path to establishing GHD involves several steps:

- history (family, gestation and birth, individual),
- clinical investigation,
- anthropometrical (growth) evaluation,
- static biochemical tests,
- GH-related basic biochemical investigations,
- evaluation of GH secretion,
- imaging techniques,
- molecular genetics.

Commonly, the initial suspicion of GHD is proposed by a general practitioner or family physician, who observes signs of impaired growth; while the conclusive diagnosis of GHD is confirmed by paediatric endocrinologists in tertiary institutions. Therefore, in some medical environments, the criteria for referring such children from a lower level of child care to experts may differ from the criteria used by specialists to confirm GHD (24, 25).

Due to the complexity related to diagnosing and classifying GHD in childhood and adolescence, in particular in the less severe, non-acquired forms, a number of controversies had arisen which led to numerous publications by specialists, societies and expert groups over the years (26–30). In the

author's view, there are only a few aspects which are of particular significance in diagnosing and treating GHD during the main phases of growth - infancy, childhood, and puberty (which partly overlap) (31) – these will be considered in detail here.

GHD IN INFANCY AND VERY EARLY CHILDHOOD

While – in simplistic terms - postnatal growth during the childhood phase is apparently driven by parameters of the GH-IGF system, prenatal growth is primarily influenced by the insulin-nutrition environment. During the first months of life, GH blood levels are high, while those of IGF-I are low, presumably due to lower GH sensitivity during the growth phase of infancy, which, when it fades, is accompanied by an inverse trend: decline of GH and increase in levels of GH-dependent hormones (e.g., IGF-I, IGFBP-3) (32, 33). The dynamics of growth and the GH-IGF system during infancy and early childhood pose specific problems when diagnosing GHD during this period of life. In contrast to later childhood, the suspicion of GHD in the neonatal period is commonly neither driven by severe smallness at birth (34) nor by poor postnatal growth, but often by normo-insulinemic hypoglycaemia or/and protracted postnatal icterus (with elevated direct bilirubin), or/and underdeveloped external genitalia (phallus, clitoris, maldescensus testis). Besides hypoglycaemia, the other signs are commonly only present in the additional absence (also prenatally) of other pituitary (TSH, LH, FSH, ACTH) hormones.

Although conventional techniques to quantify GHD secretion as described below are generally not applicable during this phase of life, the diagnosis of GHD in suspected cases can be established without dynamic tests. Indications of GHD can be ascertained by means of basal IGF-I measurements and/or IGFBP-3 of < - 2 SD (sensitivity of 80%) (35) and *via* tests of GH levels using single serum drawn during hypoglycaemia (GH < 20 ng/mL) (36). In infants and toddlers very low normal levels of IGF-I make it difficult to distinguish normal from GHD (16). Therefore IGFBP-3 is the preferred diagnostic tool at this age. Additionally, filter paper samples used for neonatal screening also offer clues (GH < 7 ng/mL) (37), as does a series of low, randomly-measured GH levels.

Growth in infancy is very dynamic: body length at 2 years is about 40 cm greater than at birth. Height velocity (HV) decreases from about 25 cm/year during the first year to about 12 cm/year during the second year (38). About 50% of infants with congenital GHD deviate from the infancy component of growth (39) and height after one year declines below normal limits (40). However in many cases in which GHD was detected during childhood, low height velocity could have previously been observed in infancy (41, 42). On the other hand, feeding difficulties and failure to thrive may be misleading symptoms in terms of GHD. The careful evaluation of length and weight during regular post-natal care could thus lead to an increase in the fraction of children with suspected/diagnosed GHD at an early age.

Children who are diagnosed very early in life often suffer from a congenital disorder (cGHD), such as anatomical defects in the hypothalamic-pituitary region (e.g., pituitary stalk interruption syndrome [PSIS]), which can be visualized by means of neuroimaging (43) or by identifying other genetically-caused disorders (44, 45). Such cases are often associated with combined pituitary hormone deficiencies. Whether or not perinatal head trauma is a possibly relevant cause of GHD acquired at birth, as suggested in the past (46), is yet to be clarified. Differences in the characteristics of very young children with GHD as compared to those during childhood have been documented in a few series (47–49) and are listed in **Table 1**.

NON-ACQUIRED GHD DURING CHILDHOOD

Anthropometry

It is the observed deviation from normal growth – from about two years of age to the onset of puberty – that typically initiates exploratory steps towards diagnosing GHD. A comprehensive analysis of growth must include measurements of height, weight, head circumference, and other anthropometrical data to determine body proportions (e.g., sitting height, arm span); in

TABLE 1 | Characteristics of very early onset of GHD compared to childhood onset.

Age group		0-1 year	0-3 years	0-2 years	6-8 years
Authors		**Huet et al. (1999) (47)**	**Cetinkaya et al. (2017) (48)**	**Ranke et al. (2003) (49)**	
N (m/f)		59 (33/26)	67 (37/30)	234 (154/80)	1,498 (1.004/494)
Birth Length	SDS+	-0.9	-1.0	-0.6	-0.5
Breech delivery	%	–	6	10.7	4.8
Age	yrs*	0.5^{+}	1.2^{+}	1.4	6.9
Bone Age	yrs*	–	–	0.8	4.5
Length/Height (Ht)	SDSCA+	-3.5^{+} +/-1.9	-3.9 +/-1.3	-3.5	-2.4
Ht - tHt	SDSCA+	-3.1	–	-3.3	-1.8
Test: maxGH	ng/mL*	2.2^{+}	1.0 (0-6.5)	4.0	6.5
Hypoglycemia	%	85	–	30	3
Microphallus	%	$52^{\&}$	–	28	2
Isolated GHD	%	15	25	50	86

**median; $^{+}$mean; $^{\&}$male only.*

addition, it is also imperative to apply methods to estimate the relative amount of fat mass (e.g., BMI, fat fold thickness, DXA). In order to visualize and/or calculate the extent of any deviation from normal values, appropriate references need to be applied. For the assessment of height, there are up-to-date and ethnically-appropriate references, which are commonly available for the corresponding population; and, in parallel, SD scores for chronological age (Ht SDS_{CA}) should be calculated. By convention, a height measurement below –2.0 SDS_{CA} defines short stature for a given population. In order to determine height in relationship to parental height, a familial "target height" must be calculated and transformed into an SD-score (THt SDS) based on the same references (50, 51). This information is then used to calculate the child's height, corrected for its parental target height (cHt SDS_{CA} = Ht SDS_{CA} - THt SDS). A cHt below –1.3 SDS_{CA} (equivalent to about the 10th centile), roughly denotes shortness outside the familial range. It is remarkable many recent national guidelines do not recommend cHT as a diagnostic criterium (25).

Height velocity [HV] - the change of height over time (cm/year) – expresses the dynamic growth process and is considered the "golden parameter" for any growth evaluation. However the calculation of HV necessitates taking a minimum of two height measurements in 3, 6 and 12-month intervals. The time required between two measurements, in order to obtain an accurate result, is a function of the underlying HV [the greater, the shorter] and the error of Ht measurement [the smaller, the shorter]. The HV SDS_{CA} is calculated on the basis of appropriate numerical HV references, deriving from (difficult-to-obtain) longitudinal investigations (52). Moreover, the complex dynamics of height velocity over time, plus the common delay in developmental tempo in GHD, as evidenced by a delay in bone age [BA], makes HV - and even more so HV SDS_{CA} - a diagnostic tool prone to error. Therefore, it is difficult to clearly distinguish between normal HV and one that is too low in children with suspected GHD. However, a HV SDS_{CA} > -1.0 SDS (approx. 25th centile) is considered to be unlikely during childhood, in the context of non-acquired GHD (25, 26). A practical and probably more robust surrogate measure for HV is the change in height, expressed in terms of delta $HtSDS_{CA}$, derived from two Ht measurements taken 6-12 months apart. A decrease in delta Ht SDS (deflection) of >0.25 SD over one year is considered to be a strong indicator of true growth disorder during childhood (53, 54). Since the diagnostic procedure for childhood non-acquired GHD often takes several months, and considering that height measurements were frequently documented in the past, it became evident that the inclusion of HV parameters strengthens the diagnostic process without unduly delaying treatment.

The appearance of a child with severe GHD can be conspicuous: there may be puppet-like features, with a relatively large neurocranium, slight truncal obesity, and small hands and feet, among other characteristics. However less attention has been given to the measurement of various relevant anthropometrical features and to compare them with the height data (in terms of SDS_{CA}) of normal and short children (55, 56). Only few comprehensive references have documented a great variety of anthropometrical variables in children simultaneously (38, 57). Although such references may not match the population of the child in question, they need to be applied in order to ensure complex anthropometrical analyses. If different normative references for each parameter (e.g., height, weight, arm span) are used in calculating SD scores, a false picture will emerge. Investigations of body composition with the help of modern tools, such as DXA, BIA, CT and MRI, provide evidence of the negative change in the muscle to fat mass ratio that is typical for GHD children.

An x-ray of the hand and wrist is done to evaluate bone maturity [transformed into bone age (BA)]. If possible, it should be determined automatically in order to avoid a rater bias (58), but also to detect a primary bone disorder, as part of the evaluation for GHD. It is important to remember that, in GHD, a BA [yrs] > (CA – 1) [yrs] is not likely to be found in true GHD during childhood (59, 60).

Insulin-Like Growth Factors

The two most important GH-dependent static peptide hormones in blood that must be measured during the diagnostic work-up of GHD are insulin-like growth factor-1 (IGF-I) and the IGF-binding protein-3 (IGFBP-3). They are part of a complex system that regulates cellular growth (13). The immunoassay is a well-established method for measuring these peptides in body fluids (61, 62) and reference values of basal blood levels over the whole human age spectrum in both sexes have been established by means of various assays (16, 63, 64). Based on the results of IGF levels in blood, further GH testing may be required in short children in order to obtain compelling evidence for the true existence of GHD. The interpretation of IGF levels measured by means of this biochemical diagnostic process must include the results of the above-mentioned clinical and anthropometrical investigations (65).

There is a wealth of literature on the diagnostic utility of IGF-I and/or IGFBP-3 measurements in the case of childhood GHD (16, 66, 67). In most of these studies, groups of children with GHD, based on various results of diagnostic tests, were analyzed. The IGF results in groups with (often isolated idiopathic) GHD were compared with groups of children with similar clinical characteristics but who had been classified as non-GHD (e.g., idiopathic short stature [ISS] (68, 69). The criteria for the anthropometric work-up and the static biochemistry in the studies with patients during mid- to late childhood were not uniform; in addition, the modalities of GH quantification (assays, test procedures) and cut-off levels to tests (commonly between 5 and 10 ng/mL) varied between studies. Nevertheless, the overall results from studies in which a cut-off of 10 ng/mL of GH (maximum) was implemented show a rather uniform qualitative picture: For both IGF-I and IGFBP-3 (expressed as an SD score for age), a cut-off of about -2.0 SDS denoted lower sensitivity (the power to correctly confirm GHD) than specificity (the power to correctly exclude GHD) (16). Thus a normal level is likely to exclude GHD, but below normal levels do not prove GHD. When a GH test cut-off of 7-8 ng/mL was accepted as evidence of GHD in childhood, IGF-I levels of < -1.4 SDS demonstrated a sensitivity of 100% and a specificity of 33%. In the same cohort investigated, a

IGFBP-3 level of < -0.2 SDS showed a sensitivity of 100% at a specificity of 14% (70). In many countries, an IGF-I level of < - 2.0 SDS is a requirement for the diagnosis of GHD during childhood (25). However, a note of caution should be given here: the reference ranges reported for children ensued from a number of different assays, which is why the derived SDS_{CA} values of IGF-I or IGFBP-3 may differ considerably. New approaches for establishing multidimensional references may be developed in the future (17).

DEFINING IMPAIRED hGH SECRETION

The core issue for the diagnosis of GHD is to obtain proof of impaired GH secretion. This entails determining hGH in blood as well as exactly quantifying GH secretion in normal and short children. The possibility to measure minute quantities of hGH in blood, for clinical purposes, started with the first immunoassays in 1963; and a process of methodological refinement has followed ever since (71–73). This process has involved, among others, the development of international reference preparations - from pit-hGH [IRP 66/217; specific activity approx. 2 I.U./mg] to authentic r-hGH of the 22 kD variety [IRP 98/574, specific activity 3 I.U./mg] (74), in addition, it has advanced from the use of polyclonal antibodies to very specific monoclonal antibodies for (22 kD hGH) detection. Modern assays do not determine all GH variants, which may have biological functions different from 22 kD hGH (75).

The discovery of the pulsatility of pituitary GH secretion led to the recognition that it is not possible for single measurements to represent the overall amount of GH secreted. Consequently, the total daily amount of GH secreted began to be quantitated by means of various procedures over the whole age range (76, 77). Groups which used spontaneous GH secretion for the evaluation of the GH secretory status in children mostly took a frequent sampling approach (e.g., every 20 or 30 minutes) over 8-12 hours of sleep; and considered a maximum GH level of > 7 ng/mL and/or an integrated level of > 3 ng/mL) to be the approximate borders of normality in prepubertal children (70, 78). However this approach was not held to be feasible by most physicians involved in diagnosing GHD proper in pediatric endocrine practices (26). Nevertheless, the quantitation of spontaneous GH secretion remains a prerequisite for diagnosing one variety of GHD, namely, neurosecretory dysfunction (79).

The discovery that hypoglycemia can provoke a GH release, the magnitude of which can be taken as a surrogate for the secretion capacity (80, 81) initiated the identification of many such stimuli (36) which found their way into our clinical routine. However the mechanism of GH stimulation through such agents differs from their "stimulatory power", due to the fact that their effects may also vary, depending on their susceptibility to metabolic and other influences (36, 82–84). In the search for a parameter that reveals normal/too low GH secretion in patients, clinicians opted for a plain and simple answer: the maximum level observed during a test. This set off the ongoing debate about "cut-off" levels, which basically depend on the GH assay and test procedure used. The low repeatability of all types of stimulation tests was acknowledged and the medical community agreed upon accepting only the maximum level of two tests in differentiating between GHD and non-GHD. In "standard" tests, a maximum level of >5- 10 ng/mL was accepted as normal in prepubertal children; on the other hand, it was recognized that test procedures involving GH-releasing hormone (GHRH) provoked a release of pituitary GH, which is about 2-4 fold higher than that seen in "classic" tests (85).

Since the amount of GH secreted spontaneously or through stimulation depends on other factors, such as age, sex, pubertal stage, body composition and nutritional stage; and also varies individually from day to day, it remains a very difficult task to establish normal references. Moreover, each child may also have an inherent set point of GH secretion for maintaining physiology. Thus, in order to define GHD in children by means of a complex diagnostic process, it is expedient to apply a cut-off range for GH levels rather than use a single cut-off.

GHD: DIAGNOSIS AT EARLY PUBERTAL AGE

Anthropometry

At the time when puberty can be expected in normal children (86, 87), short children do not exhibit signs of puberty. Thus during this period, it is particularly difficult to differentiate between true GHD and idiopathic short stature (of the variety with pubertal delay) or hypogonadism (88). The diagnostic problems are mainly related to (1) establishing the onset of puberty, (2) the evaluation of growth, and (3) the issue of how to determine an impairment in GH secretion.

Tanner introduced the globally-used standards for the clinical stages of puberty (89). The onset of puberty in girls can be determined by palpating breast tissue, not by inspecting the breast, since breast tissue growth is an effect of estrogen. In boys, the onset of puberty is assumed at a mean testis volume of ≥4 ml, the volume being predominantly an indicator of an increase in the testicular seminiferous structures and not testosterone production. Testis volume is commonly estimated by comparison with an orchidometer (90). These procedures are prone to inaccuracies, which are not eliminated by applying new methods like sonography. The analysis of a pubertal growth spurt by means of mathematical algorithms (91–93) has shown that the onset ("take-off) of puberty - which is driven by hormones - is an exact indicator and may occur 6-36 months before the clinical signs mentioned above are evident.

For the diagnosis and quantification of a growth disorder, it particularly relevant to adequately compare an individual's height with normative height references. According to historical data devised by Marshall and Tanner (86, 87), the pubertal stage B2 in girls normally occurs between about 8 und 13 years of age, whereas the pubertal stage G2 in boys normally occurs between about 10 and 14 years of age. The normal take-off of the pubertal growth spurt occurs at about 8-11 years of age in girls and 10-12 years of age in boys (38). Thus, in clinically prepubertal children, a height deviation from normal at pubertal

age – expressed in terms of $HtSDS_{CA}$ - is falsely exaggerated, since the normal growth curve has left the childhood path and is dominated by the pubertal component of growth (93). A Belgian survey showed that 19% of 295 children diagnosed with IGHD were ≥ 11 years of age; similar results - 17% of 156 children - were found in a German study (21, 23). In these children, height should rather be compared with data based on childhood references that have been extrapolated (adjusted) into the pubertal age range (94, 95). It is not known whether bone age - instead of CA – would be suitable to correct the error of HtSDS calculations based on CA. This aspect is even more relevant in terms of height velocity, for which adjusted HV references are available (96). Height velocity shows a marked prepubertal nadir which is more pronounced the longer puberty is delayed (38, 97). This is why, in the author's view, a low HV should be interpreted with great caution in children during the pubertal age. These anthropometrical considerations can be effective in correcting the calculated growth parameters for delayed puberty and may increase the likelihood of classifying short children correctly before biochemical testing is done. For the static GH-dependent parameters, IGF-I and IGFBP-3, which also increase during hormonal puberty take-off, similar considerations should apply; in addition, adjusted references should be published in order to avoid the falsely low calculations of SD scores for age. This may avert inappropriate treatment being given on the basis of incorrect (false positive) classification of isolated naGHD during the pubertal age.

Impaired GH Secretion and Priming

The next and even more strongly debated issue is the question of how to interpret GH test results during the pubertal age. Puberty onset varies between populations, but as discussed above, starts at the earliest at about 8 years in girls and 10 years in boys and is accompanied by marked hormonal changes (98, 99). We know today that the amount of GH secreted is augmented during puberty, as a result of estrogens secreted in both sexes (100). While there seems to be no major change in GH secretion during mid-childhood, the total amount of spontaneously secreted GH during puberty is increased (78) as are the maximal levels of GH observed in varying test procedures (36, 101, 102). Logically, this means that higher cut-off levels should mark subnormal GH secretion in pubertal (GHD) children. In contrast, a (short) child who is still prepubertal during the pubertal age may secrete GH amounts considered to be too low – but only on grounds of non-existing puberty. The same reasoning applies for the static IGF parameters that are not adapted for delayed puberty.

To avoid such misclassification, it was proposed that GH testing in these children should be conducted after exposing them to sex steroids (called "sex-steroid priming") to briefly induce sex steroid augmented GH secretion (103). Unfortunately, this procedure, involving short exposure to estrogen (in girls) or aromatizable androgens or estrogen (in males), is not standardized. Nevertheless, it has been shown that such priming leads to enhanced maximal GH levels in tests (36, 103, 104). However the endocrine community is still divided on this issue (25, 26, 105, 106). It is likely that the wish to diagnose non-acquired GHD at pubertal age will diminish when the anthropometric and other tools mentioned above are valued for facilitating the correct interpretation of data in the context of naGHD. Some examples of characteristics of children at the timepoint of diagnosis, recorded over the past 50 years, are listed in **Table 2** (107–110).

TREATMENT OF GHD WITH hGH

Aims of GH Treatment

In GHD, replacement with hGH aims at the normalization of deviant aspects of growth, body composition and body function. In children and adolescents, the issue of hGH efficacy is primarily associated with growth: rapid catch-up growth, normal

TABLE 2 | Characteristics of children and adolescents with non-acquired GHD (idiopathic GHD [IGHD] plus congenital GHD [cGHD]) at diagnosis).

hGH available		**pit-Hgh National Institution**			**pit-hGH commercial**	**r-hGH**		
Qualifying hGH Test Maximum		**< 5.0 ng/mL**			**<7 ng/mL**	**< 10 ng/mL**		**<7-8 ng/mL**
Author		**Soyka et al. (1970) (Boston) (107)**	**Prader et al. (1970) (Zürich) (108)**	**Aceto et al. (1972) (USA) (109)**	**Ranke et al. (2018) (Tübingen) (110)**			
Period -Years		<1970	1960-70	<1972	1968- 87	1988-97	1998-07	2008-15
Parameter								
N		15	7	52	87	112	331	45
Age (10th-90th centile)	yrs*	8.7	8.0	11.2	8.2 (4.0-15.3)	5.6 (2.9-11.9)	6.7 (4.1-13.5)	5.1 (2.5-10.6)
BoneAge	yrs*	na	4.6	5.9	4.4	3.8	4.8	4.2
Height (Ht)	SDS_{CA}+	-5.0	-4.7	-5.8	-4.3	-3.3	-2.9	-3.1
Ht-velocity	cm/yr*	2.8	2.5	3.4	4.7	4.9	5.1	5.3
deltaHt	SDS_{CA}+	na	na	na	-0.14[a]	-0.23[b]	-0.04[c]	-0.23[c]
Test: maxGH	ng/mL*	<3.1	na	<10	4.1	5.8	5.1	4.2
IGF-I	SDS_{CA}+	na	na	na	-2.9	-3.2	-2.6	-4.8
IGFBP-3	SDS*CA*+	na	na	na	na	-2.7	-1.0	-3.4
Isolated GHD	%	na	na	na	40	63	77	82

Median; +Mean; comm, commercial production; [a]n = 32; [b]n = 52; [c]n = 214; [d]n = 36; na, not available.

maintenance growth, appropriate timing and magnitude of pubertal growth, and the achievement of an adult height within the normal range. In addition, efficacy in children with GHD should also include the achievement of normal body composition and functioning, as well as the normalization of biochemical abnormalities associated with GHD during post-adolescence and throughout adult life.

Dosing and Mode of Application of hGH

The first patient to receive pit-hGH through Maurice Raben was initially given 1 mg, injected twice a week (b.i.w.) i.m.; later, the dose was raised to 3 mg, three times per week (t.i.w.). Raben administered his pit-hGH powder after reconstituting it in solvent (3). In subsequent years, pit-hGH units were devised, based on the growth response as well as the results of bio-assays using hypophysectomized female rats (111). More refined methods of purification led to a product with a potency of about 2 IU/mg (112). A dose effect in GHD – 5 IU b.i.w. *vs.* 10 IU b.i.w. - was observed by Preece et al. (113) Frazier described a linear-log relationship to the induced height velocity that resulted from doses ranging between at least 30 mIU/kg and 100 mIU/kg body weight t.i.w (114). The potency of recombinant hGH preparations was validated against international reference preparation with modern assays: 2.6 IU/mg for meth-r-hGH and 3.0 IU/mg authentic r-hGH. The amount of GH secreted - as evaluated by deconvolution analysis - was estimated to be about 20 μg/kg per body weight/day before puberty and about twice as high thereafter (76). The current starting doses of r-hGH, approved by authorities for prepubertal children, vary between a range of about 25-43 μg/kg body weight per day (115, 116) but may exceed this margin during puberty.

Pit-hGH was often administered using the total content of one ampule (2-4 IU), 2-3 times i.m. per week. After studies showed that the same amount could result in higher growth rates – in the long and short term - by dividing it into daily injections (117–119), daily s.c. injections became standard practice. GH doses are calculated either according to body weight (amount/kg BW) or per body surface (amount/m^2 BS), with the latter precluding overdosing in obese patients. Today, exact doses can be applied easily with the help of "pens", which may also allow monitored self-application (120). The role of long-acting GH variants for the treatment of GHD will be evaluated in the future (121).

Adherence

Adherence (compliance) is an essential prerequisite for any therapy to be effective. The risk of non-adherence in GHD is high, because GH must be injected daily (by proxy or by patients) over many years. Great differences were found – mostly in short-term growth - in studies on this subject, particularly in terms of the method of recording adherence, the characteristics of the cohorts investigated and the quantification of missed injections (122–125). Generally, the level of adherence appears to be high during the important but less dose-dependent first year of treatment (126), but it is lower thereafter, particularly in independent adolescents (127). Even one missed dose per week during the first treatment year in children results in a loss of height gain of 0.11 SD (122), a number which adds up to a substantial figure over time. Due to the great heterogeneity of causes (e.g., discrepancy to expectation, social circumstances, injection problems), strategies to prevent non-adherence must be individually adapted (121, 124, 127, 128).

EVALUATION OF THE GROWTH RESPONSE AND RESULTS TO GH THERAPY IN GHD

There have been roughly four phases of GH treatment from the time treatment with pit-hGH was first reported in 1958: (a) the experimental phase with pit-hGH (1958-approx. 1962), (b) the era of greater availability of pit-hGH (1962-1985), (c) the early era of r-hGH (1985–2000), and (d) the "consolidated" era of r-hGH (> 2000). The total growth process during GH treatment of GHD, starting with prepubertal age, can be divided into: (a) the initial phase of the first 2-3) years, which mark the phase of catch-up growth, (b) the childhood growth phase and (c) the pubertal growth phase, that ends in (d) the period in which (near) adult height is reached.

PREPUBERTAL GROWTH PHASE

Response Evaluation

The response to GH treatment is mostly analyzed in annual intervals and can be expressed in terms of height velocity (HV; cm/yr), change in HV in comparison to a previous period, HV SDS_{CA} and the resulting change (delta HV SDS_{CA}) (129) or in terms of delta HT SDS_{CA} calculated over a certain period of time with treatment (prepubertal years, total puberty, start of GH to NAH). Pure HV (cm/yr) is a robust term and also practical as it can be visualized in a growth chart; however, it provides little exact information when measurements exceed the normal range. The expression of HV in terms of SD scores or changes over time is problematic, particularly during infancy and the pubertal age. During the catch-up phase and over longer periods of time, growth can also be described by means of mathematical algorithms (130–134).

Several cut-off levels for distinguishing between a normal and poor response during the first treatment year have been proposed: a change of ≥ 3 cm/year in HV as compared to pretreatment values (135), HV SDS ≥ mean – 1 SDS (136), HV SDS (for sex and age in normal children) ≥ + 1 SDS (52), delta Ht SDS ≥ +0.3 SDS or +0.5 SDS (137, 138). However comparisons led to inconsistent results (139).

Empirical Response Targets

Rather than using normal references for evaluating the response to GH, it was proposed that results should be compared with the response of other treated patients. Based on large numbers of treated prepubertal children, who were observed in pharmaco-epidemiological surveys (NCGS and KIGS), references for HV (cm/yr) or delta Ht SDS were published (136, 138). These "height velocity targets (HVT)" took into consideration the diagnosis,

sex, and age in prepubertal children from 4-13 years of age, but examined only the mean GH dose of the cohort. Based on NCGS data (136), HV targets were devised in graphical terms for both male and female children with IGHD and OGHD (maximum GH in tests: <10 ng/mL) for the first treatment year. The mean GH dose given was 0.30 mg/kg per week. Based on KIGS data (138) references for HV and delta Ht SDS were presented as graphs as well as numerically for prepubertal children with both severe (maximum GH in tests: < 5 ng/mL) and less severe (maximum GH in tests: 5-10 ng/mL) GHD, during the 1st and 2nd treatment year. The mean GH dose given was 0.22 mg/kg per week. The HVs of the GHD cohorts in the NCGS study were very similar to the HVs of the "severe" GHD cohort in KIGS.

Growth Prediction

Another approach to evaluate the response of a treated patient is to compare the response variable (e.g., HV (cm/yr), delta Ht SDS) during a certain growth phase with the most likely expected response (and its error, at the start of each treatment phase) based on prediction algorithms derived from large cohorts. The advantage of this approach, as against using HVTs, is that validated prediction models consider a multitude of characteristics of an individual, the most important being the individual GH dose applied. The problem is to keep the error of prediction as low as possible. This error tends to rise when an increasing number of predictors that are not standardized are included. Several approaches have been used to develop prediction models (140–145). The observed and the predicted growth response can be compared and the difference can be expressed in terms of an 'index of responsiveness' (IOR) = [(observed response –predicted response)/error of prediction], which is a surrogate for the potential of an individual to respond (responsiveness) to GH, as compared to matched patients. An IoR below –1.0 denotes a poor response. Prediction models for various growth phases and diagnoses have been developed (145, 146) and are also available in the form of a software medical device (147). Prediction models will be developed further with the emerging field of pharmacogenomics (148, 149). Their applicability will expand with the growing importance of new electronic (self-)learning tools in medicine and in terms of optimizing cost-effective treatment.

Apart from the growth response, IGF-I targets have also been proposed as a means to guide and optimize dosing (150–153). Advocates of this approach point out that it offers a more cost-effective use of GH. Overall, the evaluation of the response to treatment, regardless of the tools used - particularly but not exclusively during the first phase of treatment - is of great importance in order to ensure an optimal outcome of growth in a treatment strategy which includes the prevention of non-adherence and an efficacious use of GH.

PUBERTAL GROWTH PHASE

Clinically, pubertal growth is the phase between the first appearance of clinical pubertal markers – breast in girls, testis volume in boys – and the end of growth due to the closure of the epiphyses of the long bones (89). In practice, the near end of growth is commonly assumed if the HV is below 2 cm/year and bone age is above 14 years in girls and 16 years in boys (154). Since hormonal changes take effect before clinical markers are noticeable, the pubertal growth phase is actually longer (95, 155, 156). Pubertal growth is governed by the interaction of sex steroids (estrogens and androgens in both sexes) with the activated GH-IGF system (100, 157) and its combined effects on the skeletal growth targets (158, 159). Several specific issues exist with respect to GHD treatment during pubertal growth: the GH dosing, the timing and length of puberty (starting age *vs*. end of growth) and the choice of sex steroid in the case of gonadotropin deficiency.

Bourguignon (160) discovered that total pubertal growth (TPG) is inversely correlated to age at onset of puberty in normal children, but that this did not affect final adult height. This means that the partial contribution of pubertal growth to total growth is inversely correlated to the prepubertal fraction. Accordingly, in idiopathic GHD (non-acquired GHD), TPG was found to be *positively* correlated with HT at puberty onset and at age at the end of growth and *negatively correlated* with age at puberty onset and that GH dose only has a minor effect (161). Mauras showed that a doubling of the prepubertal GH dose during puberty, over four years, results in only about 4 cm of additional gain in TPG (162). Thus, the extra gain in height by means of r-hGH during puberty is much more expensive. Results of studies comparing males and females with spontaneous or induced puberty showed a smaller gain in the induced groups, since they were older at puberty onset (**Table 3**) (163–165). However the lower pubertal gain in females is probably the result of sub-optimal estrogen replacement, in terms of timing, dose and preparation (166). Considering the fact that TPG only accounts for about 20% of total postnatal growth, the aim should be to normalize height well before puberty onset. It is a common observation that the relative height attained in terms of SD scores for age at puberty onset can be maintained even with prepubertal GH doses. Delaying puberty onset and prolonging the whole pubertal phase - with drugs suppressing puberty, such as GnRH (167) and/or increasing GH doses at puberty onset (e.g. doubling the dose over pre-pubertal levels) - are approaches to be considered in individual cases with non-acquired GHD as a kind of "rescue attempt" to improve adult height. By doing this, however, the well-known phenomenon of the acromegaloid phenotype of puberty may also be overly augmented.

ADULT HEIGHT REACHED

Several reports were published after years of treatment with pit-hGH in which the adult height outcomes achieved in non-acquired GHD (often called IGHD) were described. These results were summarized in reviews (168–170). As exemplified in **Table 4**, (169, 171–174, 176) these patients had been severely GH deficient (maximum in tests < 7.5 ng/mL) and were relatively old (approx. mean age: 13 yrs) at diagnosis and GH start. These

TABLE 3 | Examples of height in children with non-acquired GHD: start GH, puberty onset (spontaneous *vs*. induced), near adult height (NAH).

		Ranke et al. (1997) [KIGS] (163)				Thomas et al. (2001) [Belgium] (164)				Maghnie et al. (2006) [Italy] (165)			
		male		female		male		female		male		female	
		Pub spon	Pub ind.	Pub spon	Pub ind.	Pub spon	Pub ind.	Pub spon	Pub ind.	Pub spon	Pub ind.	Pub spon	Pub ind.
N		66	51	64	14	25	7	24	5	26	31	31	18
GH start		median				mean				median			
maxGH to tests	ng/mL	<10				<10				<10			
Age	yr	10.5	9.9	9.9	6.8	12.4	14.4	10.6	11.5	8.0	6.5	7.7	10.5
Ht	SDS_{CA}	-2.7	-2.8	-2.9	-2.7	-2.7	-2.9	-2.7	-2.9	-3.0	-3.0	-2.6	-3.6
targtHt	SDS	-0.4	-0.7	-0.1	-0.4	-0.8	-0.1	-0.8	-0.1	-0.4	-0.5	-0.6	-0.4
GH dose	IU/kg	0.57				0.5-0.7				0.60			
GH (inj./wk)		r-hGH (2-7)				r-hGH (7)				r-hGH (5-7)			
Pub start													
Age	yr	13.8	14.9	12.9	13.7	13.3	17.2	11.8	14.9	13.4	14.9	12.6	13.5
Ht	SDS_{CA}	-1.6	-1.3	-1.4	-1.0	-1.9	-1.4	-1.9	-1.4	-1.5	-2.3	-1.8	-2.3
Pub Ht gain	cm	22.5	19.6	15.0	10.4	27.5	17.1	22.2	9.6	22.8	20.5	17.1	16.5
At NAH													
Age	yr	17.8	19.2	16.0	17.0	19.1	21.0	16.2	18.5	17.6	19.4	16.5	20.0
Ht	SDS_{CA}	-1.3	-0.5	-1.2	-0.9	-0.8	-0.3	-0.8	-0.3	-0.9	-0.7	-0.4	-0.8
Ht - Ht GHstart	SDS_{CA}	1.3	2.3	1.7	1.7	1.9	2.6	1.9	2.6	2.1	2.3	2.3	1.7
Ht - Ht pub ons.	SDS_{CA}	0.3	0.7	0.1	-0.1	0.0	0.1	0.0	0.1	0.6	0.6	1.4	1.5

Ht, height; Pub, puberty; spont., spontaneous; ind., induced; ons., onset.

characteristics were not only due to a selection bias, since the oldest patients at start are the earliest to reach their (near) end of growth. On the other hand, the patients treated during the pit-hGH era were very short (mean height at GH start < -4.0 SDS) and were given dosages of about 8–12 IU of pit-hGH from various sources, injected 2-3 times per week i.m., and the total amount of one ampule often contained 4 (2) I.U. After about > 5-6 years of treatment, an adult height of about -3.0 SDS was reached in patients with spontaneous puberty, while those with induced puberty reached a height of about -1.5 SDS. Females tended to be younger and shorter at start but reached a lower adult height.

Patients during the early r-hGH era were reported to be less short (height about –2.9 SDS). With r-hGH doses of about 0.5 IU/mg/wk, injected in 3-7 fractions s.c. per week, they reached a height of about -1.4 SDS (164, 171, 175). As illustrated in **Table 4**, more recent patients who received somewhat higher doses and daily r-hGH injections reached a near adult height (NAH) mostly within the lower half of the normal range and closer to their calculated target height. However it should be remembered that in some populations there is a positive secular trend in adult height between generations in the order of about 0.4 SDS (54). Again, in such studies, females had a slightly lower height outcome. Japanese children with IGHD, who were treated with slightly lower doses compared to Europe/USA, achieved a slightly lower total height gain (176–178). Remarkably, practically all children treated as toddlers, for predominantly congenital organic GHD and MPHD, reached completely normal height (174).

TABLE 4 | Examples of groups of non-acquired GHD patients treated to NAH.

Authors		Wit et al. 1996 [review] (169)				Reiter et al. (2006) [KIGS] (176)				August et al. (1998) [NCGS] (171)		Rachmiel et al. (2007) [Canada] (172)		Westphal et al. (2008) [Sweden] (173)		Root et al. (2011) [GHD infant] (174)	
sex		m	f	m	f	m	f	m	f	m	f	m	f	m	f	m	f
GHD		Pub spon		Pub ind		iGHD		MPHD*		all		all		all		all	
N		131	31	97	30	351	200	257	172	153	195	73	23	294	107	23	24
GH start		mean				median				mean		mean		mean		mean	
maxGH	ng/mL	<7.5				<10				<10		<8.0		<10		<<10	
Age	yrs	12.8	11.6	13.8	13.5	10.1	9.3	8.0	7.2	12.0	10.9	12.4	10.4	9.1	8.0	0.8	1.0
Ht	SDSCA	-4.1	-5.1	-4.6	-4.3	-2.4	2.6	-2.9	-3.4	-2.6	-3.0	-2.8	-3.2	-2.7	-2.9	-2.4	-2.2
targetHt	SDS					-0.6	0.6	-0.3	-0.1	-0.5	-0.5	-0.4	-0.6	-1.2	-1.0	–	–
GH dose	IU/kg wk	0.2-0.5				0.6				0.9		0.54		0.7		0.9	
GH given		pit-hGH				r-hGH				met-r-hGH		r-hGH		r-hGH		met-r-hGH	
At NAH																	
Age	yrs	n.a.	n.a.	n.a.	n.a.	18.2	16.6	19.0	17.6	17.5	15.8	17.8	15.6	18.6	17.4	18.4	16.4
Ht	SDSCA	-3.1	-3.2	-1.5	-1.5	-0.8	-1.0	-0.7	-1.1	-1.3	-1.6	-1.0	-1.0	-0.9	-0.8	0.1	-0.8
Ht gain	SDS	1.3	1.9	3.0	2.7	1.6	1.6	2.3	2.3	1.3	1.4	1.7	2.1	1.8	2.1	2.3	1.4

Ht, height; Pub, Puberty; spon, spontaneous; ind, induced; GH dose, estimated from reports; iGHD, isolated GHD; MPHD, multiple hormone deficiencies [induced puberty]; all, pituitary deficiencies combined; n.a., not available.*

Several authors have examined the factors correlating with NAH by means or regression analyses (116, 164, 165, 172, 173, 175). On the whole, the results of these studies revealed certain factors that correlated positively with NAH: height at GH start, mid-parental height, duration of treatment, GH dose, and the magnitude of the first year response to GH. On the other hand, the factors correlating negatively with NAH are: age at GH start and the severity of GHD (maxGH in tests, MPHD). In randomized studies, the long-term effect of GH dosage, in terms of NAH, was only marginally positive (179, 180). This may be due to the fact that childhood and pubertal growth are evaluated together: however, during childhood growth there is high sensitivity to GH, whereas during puberty there is low sensitivity to GH. The negative correlation of the outcome with the maximum GH level to testing may also suggest that the high GH cut-off may lead to the inclusion of non-/less severe GHD patients (e.g. ISS) who exhibit overall lower responsiveness to GH treatment. The negative effect of patients with MPHD is probably the result of an inappropriate induction and/or maintenance of puberty in children with gonadotropin deficiency. This needs further evaluation.

SAFETY OF hGH REPLACEMENT IN CHILDREN

Safety issues during GH replacement may be related to the medical substance itself, may be due to the formulation of the drug (e.g. impurities, additives for drug formulation), be the result of the genuine (normal) effects (e.g., on the growth of bones, on other tissues, or be related to its metabolic action); they may be due to inappropriate dosages or a genuine incompatibility with the patient being treated (181). During the pit-hGH era, when relatively crude GH material were applied in low doses, local effects (pain, lipoatrophy) were occasionally observed (182). Due to the transmission of prions through some pit-hGH preparations, which caused the deadly Creutzfelt-Jakob disease, this era ended (183–185).

After the approval of r-hGH preparations, the analysis, detection and prevention of adverse effects became an integral part of large surveillance studies in children (186). Detailed reviews of the safety of r-hGH in children and adolescents are available (181, 187). A rare side-effect of normal GH action on accelerated bone growth in children is the slipped capital femoral epiphysis [SCFE] (188). The normal metabolic effects of sodium and water retention may cause benign intracranial hypertension (189). The anti-insulin effect of GH may cause impaired glucose tolerance or accelerate the development of DM2 in predisposed children with GHD (190). An early report associating pit-hGD with an increased risk of colonic cancer in GHD (191) raised a critical discussion about the potential role of the GH-IGF axis in cancer pathogenesis (192). A particularly controversial multinational survey on the safety and appropriateness of GH in Europe (SAGhE), which investigated mortality in adults who had received GH treatment in childhood, however presented inconclusive results (191, 193, 194). There is strong evidence that replacement with r-hGH in children and adolescents with non-acquired GHD is safe, as they receive the usual dosage range and have a low risk of other diseases (195, 196); nevertheless, it is prudent to ensure structured long-term follow-up and monitoring of IGF parameters during GH replacement (153, 187).

SUMMARY

For more than a century, it has been known that the growth hormone deficiency syndrome (GHD) affects the entire life span. Developments over many decades have led to the understanding of the key modalities, such as anthropometrical and biochemical methods, that facilitate the correct diagnosis of non-acquired – in particular isolated – GHD. However there are still a number of difficulties to overcome in order to arrive at the diagnosis as early and as properly as possible, particularly during the late childhood phase. The precise application of known techniques and principles in anthropometry as well as the prudent interpretation of test results is the imperative task of those entrusted with the medical care of children. During the past decades, replacement with GH has led to improvements in height gain during childhood and in final adult height. Yet a sizeable fraction of children does not achieve optimal adult height. Therefore the modalities for evaluating growth and the tools for adjusting treatment appropriately need to be further individualized and optimized, not only with regard to stature but also in terms of safety and costs. This entails combining the known principles of individual endocrine care with novel evidenced-based tools that substantiate the results of analyses before, during and after treatment.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Growth Hormone Deficiency and Treatment in Childhood Cancer Survivors

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Growth hormone (GH) deficiency is a common pituitary hormone deficiency in childhood cancer survivors (CCS). The identification, diagnosis, and treatment of those individuals at risk are important in order to minimize associated morbidities that can be ameliorated by treatment with recombinant human GH therapy. However, GH and insulin-like growth factor-I have been implicated in tumorigenesis, so there has been concern over the use of GH therapy in patients with a history of malignancy. Reassuringly, GH therapy has not been shown to increase risk of tumor recurrence. These patients have an increased risk for development of meningiomas, but this may be related to their history of cranial irradiation rather than to GH therapy. In this review, we detail the CCS who are at risk for GHD and the existing evidence on the safety profile of GH therapy in this patient population.

Keywords: growth hormone deficiency, growth hormone treatment, brain tumors, tumor recurrence, secondary neoplasm, childhood cancer survivors (CCS)

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INTRODUCTION

Growth hormone deficiency (GHD) is the earliest reported and most common pituitary hormone deficiency in central nervous system childhood cancer survivors (CCS), with an overall prevalence of 12.5% (1). This is a consequence of the location of the brain tumor itself, as well as treatment modality, including neurosurgery, cranial radiation, and chemotherapy agents. Radiation therapy is an independent risk factor for development of GHD, and the risk increases with higher radiation doses to the hypothalamic-pituitary (HP) axis. In addition to impaired linear growth, children with GHD have been found to have reduced cardiac muscle mass, impaired lipid profiles, and increased fat mass (2, 3). Childhood cancer survivors with GHD have similar symptoms and comorbidities to those in the non-cancer population. Patients who receive craniospinal radiation are at even greater risk for short stature than those receiving cranial radiation alone due to direct damage of the spinal radiation on bone matrix, with the greatest deficit occurring in those irradiated at younger age (4). While the overall height benefit of growth hormone (GH) treatment is dampened in those who receive spinal radiation (5), those who are treated with GH still have a significant gain in height compared to those who are not. Additionally, treatment in adult cancer survivors with GHD has been shown to significantly improve overall quality of life (3, 6).

The long-term effects of GH treatment have been extensively studied, particularly the potential association with the development of malignancy, given the mitogenic properties of GH and its

downstream target insulin-like growth factor-I (IGF-I) (7–11). This is of particular concern in CCS, as they are at higher risk *a priori* of tumor recurrence and secondary tumors. Previously, treatment with pituitary-derived GH in non-CCS was thought to be associated with increased incidence of colorectal cancer, new diagnosis of leukemia, and increased mortality from cancer overall (12–14). Since the advent of recombinant GH therapy, however, this link is not as clear (7–10). On the other hand, a French study reported an increased risk of all-cause mortality among patients treated with GH for low risk diagnoses (idiopathic GHD, short stature in those born small for gestational age, and idiopathic short stature) (15). These results, however, were from a preliminary study from only one of eight participating countries in the Safety and Appropriateness of GH treatments in Europe (SAGhE) study, a large cohort study of patients in 8 European countries treated with recombinant human GH for any indication between 1984 and 2007-2009, and were refuted in a second report from Belgium, the Netherlands, and Sweden (16). Therefore, the safety profile of GH remains an ongoing area of investigation, especially in CCS.

The aim of this review is to describe the sub-population of CCS at greatest risk for development of GHD and to highlight the most recent literature on the safety profile of GH therapy with respect to tumor recurrence and secondary malignancies in childhood cancer survivors.

DEFINING GROWTH HORMONE DEFICIENCY IN CHILDHOOD CANCER SURVIVORS

The controversy in defining GHD in CCS is two-fold. Firstly, GHD is hard to diagnose, similar to the noncancer population. Secondly, some pediatric patients who have received cranial irradiation are thought to have appropriate stimulated GH levels but inadequate spontaneous secretion, a concept called neurosecretory dysfunction. In these cases, the HP axis is unable to generate sufficient levels of GH required in children for growth in puberty (17–19). This dysfunction has not been substantiated in adults (20), but suggests that cases of GH deficiency or insufficiency in CCS may go undiagnosed. This area remains controversial due to the difficulties in defining growth hormone insufficiency, detailed below. Further, evaluation of spontaneous GH secretion is not recommended due to overlap between these GH secretory profiles in healthy individuals and those with GHD, inconsistent results, and cost and burden to the patient (2, 21).

Commonly, IGF-I levels are used in the initial diagnostic evaluation of non-CCS due to ease of measurement given the stable levels throughout the day (versus the pulsatile pattern of GH). IGF-I levels may be reduced in malnutrition states or chronic diseases, and so IGFBP-3 may also be utilized (2). However, patients with normal stature and those with short stature without GHD can also exhibit IGF-I and IGFBP-3 levels below zero SD (22). The specificity of IGF-I and IGFBP-3 levels in GHD diagnosis is about 69% and 79%, respectively in non-CCS (23), with greater sensitivity and specificity at values less than -2 SDS (24).

Some studies have reported that IGF-I levels should not be used in CCS due to poor sensitivity of IGF-I levels in patients who have received cranial irradiation (24, 25), while others have found that IGF-I can still be used as a proxy for GH function (26). Cattoni et al. supported the use of IGF-I as a screening test for GHD, as they found a statistically significant correlation between IGF-I levels and GH peak in patients who have received cranial irradiation. Even though the overall sensitivity of IGF-I was low, there was diagnostic value when the IGF-I was found to be less than -2 SDS (27). While Weinzeimer et al. also demonstrated IGF-I as not being a sensitive screening tool in children with brain tumors, the majority of their patients diagnosed with GHD had an IGF-I level below 0 SDS (28) suggesting that an IGF-I level above 0 SDS makes GHD unlikely. IGBFBP-3 is an even less reliable indicator of GHD in the childhood cancer population, where levels can be normal or above – 2 SD in up to 50% of patients. Further adding to the diagnostic difficulty is the increase in IGF-I and IGFBP-3 levels during puberty, where some have normalization of levels despite abnormal GH secretion (28). Therefore, IGF-I and IGFBP-3 may not be the most reliable indicators of GHD in the CCS population, particularly after initiation of puberty.

The recommendations for diagnosis in CCS, therefore, are the same as in the non-CCS population, which include GH provocative testing with two agents, and against relying solely on IGF-I levels (2, 21). Previously, the gold standard for diagnosis of GHD was the insulin tolerance test (ITT), however, this may be dangerous in the pediatric population due to the severe resultant hypoglycemia (22). The threshold values for peak GH after provocative testing have varied between institution and studies, with some reporting partial GHD if peak is between 7-10 ng/mL and severe deficiency if stimulated peak is < 7 ng/mL (18), while others have used a cut off of GH sufficiency if levels are > 15 mU/L (5.775 ng/mL) (29) making comparison between studies difficult.

GROWTH HORMONE AND IGF-I SIGNALING AND LINKS TO CANCER

Much of what we know about the side effects of GH and its role in cancer biology is through the study of patients with acromegaly with supraphysiologic and prolonged exposure to GH and IGF-I. Mortality rates are 2 to 2.5 times higher in patients with acromegaly, and with normalization of GH and IGF-1 levels, the mortality risk is similar to the general population (30, 31). Though controversial, patients with acromegaly were previously believed to have increased risk of cancer, particularly colorectal and thyroid cancer, as well as increased mortality from cancer overall (30, 32). A recent meta-analysis by Bolfi et al., however, demonstrated that upon control of disease (defined by normalization of IGF-1 level with varying cut-offs based on the study), the cause of death becomes similar to the general population, This analysis showed that the increased cancer incidence was for cancers not typically related to acromegaly, but instead those associated with environmental and genetic factors, as well as aging (31).

GH promotes cell proliferation, epithelial-to-mesenchymal transition, angiogenesis, and inhibition of apoptosis *via* activation of the janus kinase (JAK)/signal transducer and activator of transcription (STAT) and mitogen activated protein (MAP) kinase pathways (11, 33). The pro-tumorigenic effects of GH and IGF-I are counterbalanced by the IGF-II receptor and IGFBP-3, which have been shown to inhibit mitogenesis and stimulate apoptosis (33). *In vivo*, rats injected with pituitary-derived GH have increased number of neoplasms compared to controls, whereas knockout of the GH receptor in mammary cancer mouse models results in slower tumor growth (34, 35). Furthermore, high concentrations of IGF-I have been found in patients with prostate, colorectal, and breast cancers, suggesting that IGF-I level is correlated with risk of these cancers. The association of IGFBP-3 has not been as clear, but some have found levels to inversely correlate with risk (11, 33). It has thus been postulated that GH may promote an environment that is favorable for tumorigenesis (36), although may not be causative.

PATIENTS AT GREATEST RISK FOR DEVELOPING GH DEFICIENCY

The GH axis is thought to be the most radiosensitive of the HP axes, which is why isolated GHD may occur at lower doses of radiation (17). **Tables 1**, **2** describe risk of GH abnormality based on radiation dose and malignancy type. As such, GHD is the most common pituitary dysfunction in CCS receiving radiotherapy. The deficit is thought primarily due to hypothalamic damage rather than pituitary, as patients with radiation induced GHD still exhibit appropriate stimulated response to GHRH analogs (37, 38). Risk increases with greater total dose, decreased number of fractions delivered to the hypothalamus and pituitary, and time since radiation. A 17.3% cumulative incidence of GHD after 15 years was noted in in the Childhood Cancer Survivor Study (CCSS) (39), and GHD was present in 46.5% of adult CCS observed for a mean of 27.3 years in the St. Jude Lifetime Cohort Study (40). GHD has also been described in patients receiving targeted immunotherapy with imatinib and ipilimumab (41).

Isolated GHD can result following cranial irradiation with 18 or 24 gray (Gy) in pediatric patients with acute lymphoblastic leukemia (ALL) (18); patients treated with 24 Gy have significantly greater loss in height SDS than patients treated with 18 Gy (51). Some pediatric patients who undergo BMT for hematologic malignancy after conditioning with total body irradiation of 12 – 14.4 Gy have also been reported to develop GHD (50, 58).

Patients with primary CNS tumors receive higher doses to the CNS than patients with hematologic malignancies and so have greater risk of GHD, as well as additional anterior pituitary hormone deficiencies. Amongst pediatric patients who received an estimated 27 to 47.5 Gy to the HP axis for either CNS prophylaxis or a primary brain tumor outside of the HP region, 55% had GHD within 1 year (29). The time to onset was significantly shorter in those who received ≥ 30 Gy, and at > 5 years after radiation therapy, 100% of patients who received > 35 Gy had developed GHD (29).

Additionally, in a study of patients that included those with pituitary tumors or tumors in the region of the pituitary fossa, all patients (n=23) who received 35-45 Gy had developed GHD after 5 years of treatment (43). In a model by Merchant et al, it was suggested that GHD in pediatric patients with primary CNS tumors can occur as early as 12 months after initiation of cranial radiation therapy > 60 Gy, at 26 months with treatment doses of 25-30 Gy, and at 60 months with treatment doses of 15-20 Gy. Furthermore, in order for patients to have a <50% chance of GHD at 5 years, defined as peak GH below 7 ng/mL, the mean dose to the hypothalamus should not exceed 16.1 Gy over the course of 6 – 6.5 weeks (59).

With variation in the severity of GHD, the GH dose may also differ. Goal treatment IGF-I levels remain unclear (e.g., whether concern if above 0 SDS), but the consensus opinions for those undergoing GH treatment remain the same between the cancer population and non-cancer population and includes maintaining serum IGF-I levels within the normal range for age and pubertal status (2).

SAFETY PROFILE OF GH REPLACEMENT IN CHILDHOOD CANCER SURVIVORS

Childhood cancer survivors are at great risk of severe and life-threatening conditions, and by age 50 years, 22.5% of survivors have been shown to have two or more serious conditions (60–62). In an analysis of 14,358 patients in the CCSS, Armstrong et al. found that 1,382 patients (9.6%) developed one secondary neoplasm (SN), and 385 patients developed two SN (63). Risk factors included female sex, young age, radiation exposure, family history of cancer, and primary diagnosis of sarcoma or Hodgkin lymphoma (63).

To date, multiple large observational studies have sought to determine the risk of tumor recurrence and SN in patients treated with GH. These studies are limited by the different underlying conditions leading to GHD, difference in treatment exposures, small sample size, length of follow-up, and retrospective design. Additionally, there is lack of standardization of laboratory assays and diagnostic thresholds for GHD. Published studies do not routinely describe the severity of the GHD in the patient population or the doses of GH used. These challenges make it difficult to definitely state that there is no risk of tumor recurrence or SN, but the existing data do suggest that GH replacement in deficient individuals is likely safe. **Tables 3**, **4** describe these studies, where **Table 3** also includes patients treated with GH beyond the CCS cohort. Unfortunately the existing studies exclude those with cancer predisposition syndromes (e.g. Fanconi anemia, Bloom syndrome, Li-Fraumeni syndrome, Lynch syndrome) and so a consensus about GH treatment in this population does not exist. This population is of particular interest as they include disorders of DNA damage/repair, and as growth factors, GH and IGF-1

TABLE 1 | Radiation therapy and growth hormone deficiency in primary central nervous system tumors.

CNS Primary Malignancy	Radiation Dose	GH Abnormality	Studies
Non-pituitary brain tumors	30-50 Gy	Dependent on radiation schedule, age, length of follow-up and diagnostic thresholds; incidence may be lower if proton RT used	(42)
	> 37.5 Gy	87% at 2.5 years with GHD	
	<37.5 Gy	33% at 2.5 years with GHD	
Pituitary tumors or suprasellar region	24-56 Gy	Commonly GHD on presentation due to tumor location	
-Pituitary adenoma	35-45 Gy	Universal GHD within 5 years	(43)
-Suprasellar glioma/optic chiasmatic-hypothalamic glioma	45-55 Gy	Almost all within 2-3 years	(44, 45)
-Craniopharyngioma	54 Gy	In almost all (92%) following treatment (surgery +/- post- operative radiation)	(46)
-Germ cell tumor	24-36 Gy	Limited evidence on documented GH levels. Growth retardation on presentation with no new cases after RT	(47)

CNS, central nervous system; Gy, gray; GH, growth hormone; GHD, growth hormone deficiency; RT, radiation treatment.

TABLE 2 | Cranial radiation therapy and growth hormone deficiency in non-central nervous system tumors.

Non-CNS Primary Malignancy	Radiation Dose	GH Abnormality	Studies
Conditioning for hematopoietic stem cell transplant (leukemia, neuroblastoma)	7- 8 Gy single dose TBI	No GHD	(48, 49)
	10-12 Gy TBI	Isolated GHD in some	(43, 48–50)
CNS prophylaxis or CNS disease in acute lymphoblastic leukemia	18-24 Gy cranial radiation;	Pubertal GH insufficiency (reduced spontaneous GH secretion);	(51–54)
	12 Gy cranial radiation (for infants)	Compensated GHD (reduced stimulated but normal spontaneous GH levels); Isolated GHD in < 30%	
Nasopharyngeal carcinoma and tumors of skull base	45-66 Gy cranial radiation	GHD in almost all adult patients (96.8%) in 5 years	(55, 56)
Retinoblastoma	Estimated 13-65 Gy to HP axis	30% with GHD; 50% GHD with 20-30 Gy to HP axis	(57)

Gy, gray; GH, growth hormone; TBI, total body irradiation; GHD, growth hormone deficiency; HP, hypothalamic-pituitary.

may reduce time for DNA repair by promoting progression of the cell cycle (76).

Sävendahl et al. recently reported results from two large multicenter observational studies, NordiNet International Outcome Study and ANSWER Program, two international pharmacoepidemiological registry studies sponsored by Novo Nordisk (64). The study population included 37,702 patients, 1,149 patients with history of neoplasm prior to GH treatment. In the 10 years of follow-up, 56 patients reported 62 neoplasms. However, of these 62 neoplasms, 59.7% were considered unlikely to be related to GH treatment, 35.5% were thought to be possibly related to GH treatment and only 4.8% were probably related to GH treatment. The neoplasms documented included both benign and malignant, and the group unfortunately does not differentiate between recurrent tumors and SN. Other adverse events reported in all three groups were similar to prior reports (7, 10). Notably, the incidence of adverse events correlated with increasing risk category, emphasizing the need for close monitoring of those with high-risk illnesses including CCS (64).

Growth Hormone Therapy and Tumor Recurrence

One of the earliest individual studies to look at risk of tumor recurrence was a report in 1985 of 34 children with brain tumors, 24 of whom received GH. Thirty-three percent of patients treated with GH had tumor recurrence compared to 30% who did not receive GH (77). Due to the small nature of this study (less than 200 patients), it is not included in **Tables 3** or **4**. The similar incidence of tumor recurrence between treated and untreated groups has been supported by a number of other individual studies (72, 78–81). Mackenzie et al. compared 224 patients treated with GH to controls and found no significant difference in incidence of recurrent tumors (5.5% versus 7.3% respectively) (72). Mackenzie's study was strengthened by matching the comparison group for age, sex, radiation dose and fractionation. Rohrer et al. reported the risk of CNS tumor recurrence in 108 children treated for craniopharyngioma, ependymoma, and medulloblastoma (79). Approximately 30% of patients (13 of 44) treated with GH had a recurrence and 47% (28 of 59) patients not treated with GH had tumor recurrence, concluding that there was no association with GH treatment (79). Bell et al. reported findings from the National Cooperative Growth Study (NCGS), an open-label multicenter, post-marketing surveillance study of approximately 55,000 patients sponsored by Genentech. Of the 2,500 patients with non-pituitary CNS or extracranial malignancy prior to treatment, 99 patients had recurrent non-pituitary CNS tumors and 24 patients had recurrence of extra-cranial malignancy. The largest single group of intracranial tumor with recurrence was craniopharyngioma, with 8.7% of patients with craniopharyngioma recurrence (7). This study is limited by the inability to compare recurrence rates to those who were not treated with GH.

TABLE 3 | Post-marketing or large observational cohort studies.

Firth author, year (ref)	Study Cohort	Total Cohort size, n	Number on GH, n	Mean age at GH therapy, y	Mean duration of GH therapy, y	Mean duration of follow-up, y	Person-years of follow-up, n	Primary endpoint	Comparison group	Conclusion
Savendahl, 2021 (64)	NordiNet international Outcome Study and ANSWER Program	37,702	37.702	9.7	3.5	Not mentioned Up to 25 years	130,476	Long-term safety	Within NordiNet and ANSWER cohort	Incidence of adverse effects correlated with increased mortality risk category
Savendahl, 2020 (65)	SAGhE cohort (comprehensive)	24,232	24.232	10.5	5.0	16.5	400,229	Long-term overall and cause specific mortality	Within SAGhe cohort	Mortality not associated with mean daily or cumulative GH dose. Increased mortality risk in higher mortality risk diagnoses
Swerdlow, 2018 (66)	SAGhE cohort (Belgium, Netherlands, Sweden, UK)	10,403	10,403	Not mentioned	Not mentioned	14.9	154,795	Incidence of meningioma in GH treated patients	Within SAGhe cohort	Increased risk of meningioma following GH treatment. Greater risk in patients who received cranial radiation
Child, 2018 (67)	GeNeSIS	22,845	22,311	9.5	4.9	4.2	104,000	Standardized mortality radio and standardized incidence ratio for mortality, diabetes and primary cancer	Within the GeNeSIS cohort	Overall risk of death not elevated. Most common SN was meningioma; all patients with secondary meningioma received radiation.
Swerdlow, 2017 (8)	SAGhE cohort (comprehensive)	23,984	23.984	Not mentioned	Not mentioned	16.5 for mortality 14.8 for cancer incidence	396,344 for mortality 154,371 for cancer incidence	Cancer incidence and cancer mortality	Within the SAGhE cohort	Cancer risk unrelated to duration or cumulative GH dose
Carel, 2012 (15)	SAGhE cohort (France)	6,928	6,928	15.1 (at end of treatment)	3.9	17.3	116,403	All-cause and cause-specific mortality	Within the SAGhE cohort	Mortality rates increased, particularly in those with higher GH doses.
Savendahl, 2012 (16)	SAGhE cohort (Belgium, Netherlands, Sweden)	5,299	5,299	Not mentioned	Not mentioned	Not mentioned	46,556	Vital status, cause of death	Within the SAGhE cohort	Majority of deaths were due to accident or suicide.
Bell, 2010 (7)	NCGS	54,996	54,996	10.3 (age of enrollment)	3.6	Not mentioned	195,419 of treatment	Safety data and adverse events	Within the NCGS cohort	Overall safe profile. Craniopharyngioma was largest group of tumor recurrence.

ref, reference; GH, growth hormone; y, year; ANSWER, American Norditropin® Studies: Web Enabled Research; SAGhe, Safety and Appropriateness of Growth hormone treatments in Europe; GeNeSIS, Genetics and NeuroEndocrinology of Short Stature International Study; NCGS, National Cooperative Growth Study.

Sklar et al. were able to make comparisons in recurrence rates between GH-treated and untreated patients in the CCSS. They followed patients for a median time of 6.2 years and found 354 patients who were treated with GH (172 with primary brain tumors) amongst 13,539 total participants (73). For all patients with previous cancer diagnoses, the risk of disease recurrence was not significantly greater for those treated with GH compared to those who were not treated (RR 0.83). However, for patients with brain tumors, risk of disease recurrence was significantly reduced compared to survivors not treated with GH (RR 0.31), perhaps owing to patients with better prognosis selected for treatment with GH. Darendeliler et al. further details the recurrence rates by type of CNS tumor in the Kabi International Growth Study (KIGS) database, a Pfizer post-surveillance observational investigation of 1038 patients with CNS tumors who were treated with GH (75). Frequency of recurrence was 11.7% amongst patients with craniopharyngioma, 4.7% amongst patients with medulloblastoma, 8.8% in ependymoma group, 4.0% in germinoma, and 9.8% in glial tumors. Comparison in recurrence rates between patients who were not treated with GH was not made. There was no difference in dose of GH between patients with and without tumor recurrence (75).

Growth Hormone Therapy and Secondary Neoplasms

In the aforementioned study by Sklar et al., there were 15 subsequent neoplasm (SN) that occurred after start of GH therapy, all of which were solid tumors, and 14 occurred at a site previously exposed to external radiation or after treatment

TABLE 4 | Childhood cancer studies.

First author, year (ref)	Study Cohort	Total Cohort size, n	Median age, y	Median duration follow up, y	Number on GH, n	Median age at start of GH, y	Median duration of GH therapy, y	Comparison group	Primary endpoint	Conclusion
Journy, 2021 (68)	FCCSS	7,670	6 (at primary cancer diagnosis) 29 (at subsequent cancer diagnosis)	Not mentioned	47	Not mentioned	Not mentioned	FCSS patients matched by sex, year of cancer diagnosis, and follow-up time	Clinical and therapeutic risk factors associated with CNS SN	GH therapy not associated with CNS SN. Secondary meningioma associated with radiation.
Thomas-Teinturier, 2020 (69)	Euro2K cohort	2852	GH treated: 4; Non-GH treated: 4	GH treated: 26; Non-GH treated: 27	196	10	4	Matched by radiation dose, gender, age at first diagnosis cancer, year of first diagnosis, and follow-up duration	Impact of GH treatment on SN	GH therapy does not increase risk of SN.
Woodmansee, 2013 (70)	GeNeSIS	421	5.4	2.1	394	Not mentioned	2.9	Within GeNeSIS, non-GH treated survivors	Incidence of SN in GH-treated childhood cancer survivors	Increased risk of SN in GH-treated childhood cancer survivors. Most common SN was meningioma.
	HypoCCS	280	8.4	2.9	244	Not mentioned	6.8	Within HypoCCS, non-GH treated survivors		
Patterson, 2014 (71)	CCSS	12,098	Not mentioned	Not mentioned	338	Not mentioned	Not mentioned	Within CCSS	Incidence of CNS SN in GH-treated cancer survivors	No increase in risk of CNS-SN with GH treatment.
Mackenzie, 2011 (72)	Individual study	224	GH treated: 33; Controls: 29	14.5	224	Not mentioned	8.0	From radiotherapy database, matched by total radiation dose, age at diagnosis, duration follow-up, radiation target for primary tumor	Incidence of recurrence and SN after CNS irradiation	No increased risk for tumor recurrence or SN in GH-treated CNS survivors.
Sklar, 2002 (73)	CCSS	13,539	GH treated: 3.5; Non-GH treated: 7.2	6.2	361	10	4.6	Within CCSS, non-GH treated survivors	Risk of recurrence and SN in GH treated survivors	GH does not increase risk of tumor recurrence or death.
Ergun-Longmire, 2006 (74)	CCSS	14,108	GH treated: 3.5; Non-GH treated: 7.1	8.8	361	11	4.6	Within CCSS, non-GH treated survivors	Risk of recurrence and SN in GH treated survivors	GH-treated survivors have higher risk of SN than untreated. Most common SN was meningioma.

(Continued)

TABLE 4 | Continued

First author, year (ref)	Study Cohort	Total Cohort size, n	Median age, y	Median duration follow up, y	Number on GH, n	Median age at start of GH, y	Median duration of GH therapy, y	Comparison group	Primary endpoint	Conclusion
Darendeliler, 2006 (75)	KIGS (Pfizer International Growth Database)	1,038	7.0 – 12.1 (varied by tumor type)	5.8 (patients without recurrence)	1,038	8.0 – 12.6 (varied by tumor type)	2.3 – 2.8 (varied by tumor type)	Within KIGS database (all patients treated with GH)	Risk of tumor recurrence based on tumor type	Recurrence highest in those with craniopharyngioma. Dose of GH did not differ between patients with and without recurrence.

FCCSS, French Childhood Cancer Survivor Study; GeNeSIS, Genetics and Neuro Endocrinology of Short Stature International Study; HypoCCS, Hypopituitary Control and Complication Study; CCSS, Childhood Cancer Survivor Study; Kabi International Growth Study (Pfizer International Growth Database); GH, growth hormone; y, year; CNS, central nervous system; SN, secondary neoplasm.

with alkylating agents. They reported an increased risk of SN in GH-treated survivors, with a high number of SNs in patients with primary acute leukemia. However, when looking at malignant SN only (excluding meningiomas), the increased risk in GH-treated survivors diminished (73). This same cohort was followed for an additional 32 months with Ergun-Longmire et al. reporting 5 additional solid tumors for a total of 20 SN (74). There were no cases of subsequent leukemias. Among 13,747 patients not treated with GH, 555 SN were reported. The significant risk factors for development of SN were age at diagnosis, use of alkylating agent, radiation therapy, and GH therapy. However, when comparing patients with the same original cancer diagnosis, there was no statistically significant difference between those who had received GH and those who had not (74). In this follow-up report of GH-treated survivors, meningioma was the most common SN (9 of 20), and all patients who developed meningioma had received cranial irradiation. There was not a statistically significant increased risk of death for GH-treated patients compared to those who were not treated (RR 1.2) (74). A subsequent report of the CCSS cohort focused solely on secondary CNS neoplasms and found that GH treatment was not associated with increased overall risk (RR 1.0). Risk factors for development of secondary CNS neoplasms, including both meningioma and glioma, included increased time since cranial radiation (71).

This increased incidence of meningiomas in GH-treated patients has been replicated in several recent large studies, including the SAGhE cohort and Eli Lilly's GeNeSIS study (66, 67). The final results of the SAGhE study, reported in 2020 by Savendahl et al., showed that higher mortality risk after GH treatment was related to pre-existing mortality risk based on underlying disease (65). Preliminary reports published from the individual countries have reported on specific adverse events, including risk of new neoplasms (8, 15, 16).

In 2018, Swerdlow et al. studied 10,403 GH-treated patients from 5 of the 8 study countries and found that the standardized incidence risk (SIR) for meningioma was 75.4 (95% CI, 54.9 – 103.6) when compared with year-specific rates from the general population matched for sex, age, and country. This effect was primarily due to the higher risk of meningioma amongst those who had a prior diagnosis of cancer (SIR 466.3; 95% CI, 33.7-643.5) (66). There were 38 total meningiomas; 37 occurred in patients who received cranial irradiation. There was no significant association between risk of SN and mean GH dose, duration of treatment, or cumulative dose of GH (66).

The GeNeSIS study was a prospective observational program of 22,845 patients in 30 countries treated with GH between 1999 and 2015 (67). Amongst this patient population, there were 622 GH-treated CCS. In a study of final safety outcomes in 2018, Child et al. reported that the crude incidence rate (95% CI) of SN amongst the GH-treated childhood cancer survivors was 10.69 (13.3-21.47)/1,000 people years (67). Thirty-one patients had a SN (5.0%), and 25 of these patients had received radiation therapy during treatment for their primary neoplasm. The most common SN was meningioma and all patients with subsequent meningioma had previously received cranial irradiation (67). These studies suggest an association of GH treatment and SN amongst CCS, however, this is confounded by the established increased risk of meningiomas in those with prior brain radiation treatment (82).

Journy et al. report the risk specifically of subsequent CNS tumors in the French Childhood Cancer Survivor Study (FCCSS) (68). The FCCSS includes 7,670 patients diagnosed between 1946-2000 with a solid tumor or lymphoma (68). The risk of subsequent meningioma was 16 times higher amongst patients with prior CNS tumor than other cancer diagnoses, and the risk was significantly associated with cumulative radiation dose. However, there was no association of GH therapy with development of subsequent meningioma (68). Thomas-Teinturier et al. made similar conclusions in a 26 year follow-up of 2,852 patients identified from a separate French cohort of survivors from childhood solid malignancies (69). One-hundred and ninety-six patients in this group received GH treatment. A total of 374 patients (13%) developed at least one SN, with 40 SN occurring following GH treatment. There were none identified with subsequent leukemia, a finding that had previously been reported (74). Of the 40 SN, there were 17 meningiomas and 9 glial tumors. There was a significantly higher crude incidence of SN in GH-treated patients than untreated patients, however when adjusting for radiation dose and alkylating therapy, this

difference disappeared. In multivariate analysis, GH treatment was not associated with increase in SN risk (RR 1.2, 95% CI 0/9-2) or meningioma occurrence (RR 1.9. 95% CI 0.9-4) (69).

SUMMARY/DISCUSSION

Growth hormone deficiency may develop after radiation therapy that includes the HP region, with higher doses of radiation associated with increased likelihood of GHD and earlier onset. There are theoretical concerns about malignancy development if GH therapy is initiated if GHD is diagnosed in the CCS. However, the association between GH therapy and cancer has been extensively investigated, and while many existing studies are limited by lack of a comparison group, the current data suggest that GH therapy does not increase tumor recurrence in CCS. Some studies have suggested an increased risk of SN after GH therapy, the most frequent being meningiomas, but meningiomas are highly associated with radiation exposure irrespective of GH therapy. Overall, the safety data from studies are reassuring, but there are limitations. As long-term data are unknown, the risk vs. benefit ratio should be determined for every individual patient. Additionally, as our knowledge of the role of genetics in cancer development increases, an unanswered question is whether there is increased risk of SN during or after GH therapy in individuals with cancer predisposition syndromes.

AUTHOR CONTRIBUTIONS

NP and LC drafted the initial manuscript and revised for accuracy. All authors approved final manuscript as submitted.

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