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Human growth hormone therapy – in three stages: past, present, and future

Terapia ludzkim hormonem wzrostu – trzy etapy: przeszłość, teraźniejszość, przyszłość

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In 1921 Evans and Long reported the presence of growth-promoting substances in the pituitary glands of rats, indicating a close relationship between the pituitary gland and physical growth [1]. Engelbach in 1932 named "GH" (growth hormone) the substance extracted from the bovine pituitary and reported its effectiveness in children [2].

The start of the history of GH treatment was in 1957 when Raben extracted hGH (human growth hormone) from an acetone-preserved human pituitary gland with glacial acetic acid. Raben reported also the world`s first case of pituitary dwarfism treated with hGH in a 17-year-old boy in 1958.

In Poland pituitary extract hGH – the hormone of the first generation was applied in 1964 by Tomasz E. Romer and Irena Lenartowska.

The treatment was administered by intramuscular injection at 0.5 IU/kg b.w./week, divided into 2–3 administrations per week.

The qualification to the GH therapy was then the value of GH response in stimulation tests was of ≤ 5 ng/ml. The auxological criteria to the input of GH therapy were stronger than now, i.e. height standard deviation score (SD) of ≤ –2.5 SD in children aged < 10 years, growth rate < 3 cm/year, and bone age of ≤ 75% of the chronological age.

In 1985 multiple cases of Creutzfeldt-Jakob disease (CJD) were reported in the US and United Kingdom in patients treated with pituitary hGH (pit hGH). It was thought that many pituitary glands collected for hGH extraction might have been accidentally contaminated by the pathogen known as a prion, which caused CJD. IN 1985 the decision was made to discontinue phGH therapy [1].

The introduction of recombinant human GH (rhGH) in 1985 ended the phase of pituitary-derived human growth hormone (hGH) and its associated limitations and risks, opening the possibility of widespread clinical use.

The US is already using Somatonorm, a methionyl hGH containing methionine added by generic engineering, and phGH was removed from the market.

Very quickly the third generation of hGH was manufactured – recombinant DNA technology human growth hormone, 22 kDa, 191 amino-acid-long hGH.

The virtually unlimited supply of rhGH led to the expansion of indications for rhGH therapy, now including childhood and adult GH deficiency, Turner syndrome, chronic renal failure, small for gestational age, Prader-Willi syndrome, Noonan syndrome, SHOX deficiency, idiopathic short stature (ISS), achondroplasia, short bowel syndrome, and HIV wasting syndrome. According to the consensus from the year 2000, GHD was recognised than GH was < 10 ng/ml in two provocative tests [3].

The Growth Hormone Research Society (GRS) convened a Workshop in March 2019 to evaluate the diagnosis and therapy of short stature in children.

In most instances, it is important to ensure repeated and accurate auxologic measurements. Children should be considered for evaluation of pathology: short stature with height SDS below –2, height that deviates from the familial background, or a significant decrease in height SDS (i.e. a deflection of at least 0.3 SDS/year. However, a diagnosis of GH deficiency does not require a height cutoff, particularly in the context of very young children with hypoglycaemia and/or midline defects/pathologies or recently developed GHD.

The diagnosis of GHD remains a clinical one, where one synthesises auxologic, anatomic, and laboratory data to arrive at a diagnosis. It should not be made based solely on laboratory testing. IGF-I measurement should be undertaken using an as-

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say with reliable reference data with ranges based on age, gender, and pubertal status. Children with GHD may have delayed physical maturation, and therefore assessment of IGF-1 levels must be interpreted with pubertal status. IGF-I levels assessed in the context of pubertal status have the best positive predictive power for a diagnosis of GHD in peripubertal children. Most delegates at the workshop suggested that the threshold of GH be revised to 7 ng/ml. For GHD the starting dose is 25 μg/kg/day (0.19 ng/kg/week) in most countries in Europe.

In retesting after a therapy promoting height, the test of choice is the ITT test, and GHD deficiency is recognised at a value of GH $<$ 3 ng/ml. The therapy with GH in adults has metabolic indications and improves the quality of life of the patients.

For GHD the starting dose is 25 μg/kg/day (0.19 ng/kg/week) in most countries in Europe. The main goal of rhGH administration is to increase height velocity and adult height. The main parameter to adjust rhGH should be the growth response. The use of IGF-I serum levels may provide additional information about treatment efficacy and theoretical safety. It may also provide earlier information regarding response to rhGH than a change in height velocity. Some trials that used IGF-I based on rhGH dosing suggest that this strategy may optimise therapy in GHD and idiopathic short stature [4].

The GRS concluded that GH continues to have a good safety record when used for approved indications and at recommended doses.

Nevertheless, the GRS agreed that continued surveillance of those exposed to rhGH is essential both during and in the years after treatment, and into old age in those who continue therapy. This is particularly important with the advent of long-acting GH preparations with very different pharmaco-kinetic and -dynamic profiles compared to daily rhGH injections [4].

For many years the paediatric endocrinology community has longed for long-acting recombinant hGH formations that would decrease the inconvenience of daily injections and potentially optimise patients' compliance with such therapy. The LAGH (long-acting GH) should, at minimum, have the same efficacy and safety profile as GH administered daily while reducing the number of injections. All LAGH preparations should aim for a once-weekly treatment for GHD. Analyses of immunogenicity are ongoing. Antidrug antibodies are frequent up to 77% [5], and they did not affect safety or efficacy. No antidrug antibodies have so far shown evidence of neutralising activity which could affect the safety or efficacy. To date, there have not been additional adverse reactions noted from LAGH compared to rhGH. The use of LAGH in place of rhGH could be feasible in the future; however, there are still questions that need to be answered. Dose adjustments, the timing of IGF-I monitoring, safety, efficacy, insurance approval, and cost-effectiveness all need to be further evaluated [6].

References

1. Tanaka T. History of GH treatment in Japan. Clin Pediatr Endocrinol 2022; 31: 1–9. doi: 10.1297/cpe.2021-0044.
2. Engelbach W. The growth hormone. Endocrinology 1932; 16: 1–19.
3. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000; 85: 3990–3993. doi: 10.1210/jcem.85.11.6984.
4. Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr 2019; 92: 1–14. doi: 10.1159/000502231.
5. Grillo MS, Frank J, Saenger P. Long acting growth hormone (LAGH), an update. Front Pediatr 2023; 11: 1254231. doi: 10.3389/fped.2023.1254231.
6. Deal CL, Steelman J, Vlachopapadopoulou E, et al. Efficacy and Safety of Weekly Somatrogon vs Daily Somatropin in Children With Growth Hormone Deficiency: A Phase 3 Study. J Clin Endocrinol Metab 2022; 107: e2717–e2728. doi: 10.1210/clinem/dgac220.

