

History of GH treatment in Japan

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Highlights

- In 1975, phGH was approved for the treatment of pituitary dwarfism.
- After rhGH was approved in 1988, phGH gradually disappeared from the market.
- In 1991, rhGH was approved for Turner syndrome with GHD at 0.5 IU/kg/wk.

Abstract. In Japan, a pituitary-extracted human GH (phGH), Crescormon®, was approved for the treatment of pituitary dwarfism in 1975. The Study Group of Pituitary Dysfunction was organized by the Ministry of Health and Welfare (MHW) in 1973 and prepared the “Diagnostic Handbook: Pituitary Dwarfism” guidelines in 1974. Eligibility assessments for phGH treatment were conducted by the research group on pituitary dwarfism (later the Foundation for Growth Science [FGS] GH Treatment Eligibility Assessment Committee); however, there were 200–300 patients on the waiting list. GH treatment has been financially supported by the Grant-in-Aid Program for Chronic Diseases in Childhood, MHW, since 1974. In 1984, phGH was discontinued in the United States due to reports of the onset of Creutzfeldt–Jakob disease in patients treated with phGH. Japan approved the use of methionyl hGH in 1986 and recombinant hGH in 1988. As a result, the phGH disappeared from the market. The role of the Eligibility Assessment Committee of the FGS shifted to the provision of second opinions about diagnoses and treatment appropriateness. Since then, the indications for GH treatment of pediatric growth disorders have expanded to include other pediatric growth disorders such as Turner syndrome, achondroplasia/hypochondroplasia, etc.

Key words: phGH, rhGH, Study Group of Hypothalamo–Pituitary Dysfunction, The Grant-in-Aid Program for Chronic Diseases in Childhood, Foundation for Growth Science

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The Beginning of the History of GH Treatment

The history of GH traces back to the 1880s, with clinical reports of pituitary gigantism. Harvey Cushing, a renowned American surgeon, used the term “hypo and hyperpituitarism” in his book “The Pituitary Body and its Disorders” in 1912 to explain that short versus tall stature is caused by structural pituitary changes. In 1921, Evans 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). In 1932, Engelbach named the substance extracted from the bovine pituitary “GH” and reported its effectiveness in children (2). However, later studies have shown that bovine GH (bGH) is ineffective in humans and GH has species specificity (3). In 1941, Ray, Evans and Becks developed a GH bioassay using the tibia of rats (4). Using this approach, Li and Evans extracted and purified bGH in 1944 and reported its molecular weight to be 44,250 (5). Subsequently, Li *et al.* performed the extraction, purification, and amino acid analyses of human GH (hGH), and in 1966, they reported that hGH was composed of 188 amino acids (6), which was later revised to 191 (7).

In 1957, Raben extracted hGH from acetone-preserved human pituitary glands with glacial acetic acid (8). Raben also reported the world’s first case of pituitary dwarfism treated with hGH in a 17-yr-old boy in 1958 (9).

Around the same time, Yalow and Berson developed the radioimmunoassay (RIA) technique in 1959 to measure blood insulin levels (10). The measurement of hGH in the blood became possible when Hunter and Greenwood succeeded in labelling hGH with radioactive iodine in 1962 (11).

The National Pituitary Agency was founded in 1957 in the United States (US) to collect human cadaver pituitaries at autopsies across the nation. hGH was extracted from these pituitaries and purified at three centers, which were then distributed to researchers all over the US for the treatment of pituitary dwarfism.

In 1971, Kabi Vitrum, a Swedish semi-government corporation, collected pituitaries in Europe to extract hGH and then marketed it in Sweden under the name Crescormon®. Subsequently, the Danish company Nordisk launched the Human Growth Hormone Nordisk in Denmark in 1975.

The Beginning of the History of GH Treatment in Japan

In 1960, Dr. Kazuo Shizume and Dr. Seizo Suwa requested the Tokyo Medical Examiner’s Office to collect cadaver pituitaries in Japan. Dr. Fukashi Matsuzaki, who was studying at Dr. Raben’s laboratory at the time, extracted hGH from these pituitaries for the treatment of pituitary dwarfism in Japan. This was the beginning of GH treatment in Japan. The treatment outcomes were

presented at the symposium of the Japan Endocrine Society Annual Meeting in 1962 (12). The short-term growth-promoting effect of hGH was confirmed in a 15-yr-old boy (height, 124.0 cm) and 12-yr-old girl (height, 101.1 cm). In pediatric cases, Dr. Itsuro Hibi, Dr. Seizo Suwa, and others presented the treatment outcomes in children at the 36th Annual Meeting of the Japan Endocrine Society in 1963 (13, 14), and Dr. Suwa presented a case of GH deficiency (GHD) in a girl treated with hGH extracted using the Raben method at the Annual Meeting of the Japan Pediatric Society in 1964 (15).

Treatment using Pituitary-extracted hGH (phGH) Preparations

Human pituitaries collected in Japan from 1962 to 1974 were sent to Dr. Raben’s laboratory in the US for the extraction of phGH. The extracted phGH was used for the investigational treatment. In 1975, Crescormon®, imported from Kabi Vitrum by Sumitomo Chemical, was approved for the treatment of pituitary dwarfism and was launched in the market. The treatment was administered by intramuscular injection at 0.5 IU/kg/wk, divided into 2–3 administrations per week. As self-administration had not yet been approved, patients had to visit the hospital to receive the injections. Self-injection of hGH was approved in 1981 when that of insulin was approved for diabetes.

Prior to this, the Study Group on Pituitary Dysfunction (the Ministry of Health and Welfare [MHW] specified the disease) was organized in 1973, with Dr. Kazuo Shizume serving as the team leader. In 1974, the group developed the document “Diagnostic Handbook: Pituitary Dwarfism”. The main symptoms of pituitary dwarfism specified were as follows: 1) a height standard deviation (SD) score of ≤ -3.0 SD (≤ -2.5 SD in patients aged < 10 yr), 2) a growth rate of ≤ 3 cm/yr in patients aged ≤ 10 yr, and 3) a bone age of $\leq 75\%$ of the chronological age. The examination findings were defined as “serum GH response of ≤ 5 ng/mL each in more than two GH stimulation tests”.

For the proper allocation of phGH preparations that were imported in limited amounts, a research group for pituitary dwarfism treatment was formed in 1974, which included specialists from across the country (three facilitators and 28 members). The group created a framework for phGH allocation. Through this framework, the primary physicians of patients wishing to receive phGH submitted applications to the group for eligibility assessments, and hGH was delivered to approved physicians by a pharmaceutical company. This research group was later transferred to the Foundation for Growth Science (FGS) upon its establishment in 1977 and reorganized in 1986 as the GH Treatment Eligibility Assessment Committee. The committee formulated the “Eligibility Criteria for hGH Treatment” based on the “Diagnostic Handbook” and carried out the assessments accordingly.

In 1978, Dr. Seizo Suwa drew up a standard growth chart based on data from the national surveys of physical development of students by the Ministry of Education, Science, and Culture, and the national survey of physical development of infant and toddler by the MHW, in 1970. The standard growth chart has become widely used in the field of growth disorders. It has been revised every 10 yr according to the national survey results.

Crescormon® was added to Japan’s National Health Insurance (NHI) drug price list in January 1975. In June 1975, the number of patients assessed as eligible by the research group for pituitary dwarfism treatment was 513. However, the supply of phGH was sufficient to treat only 288 patients. Therefore, the remaining 225 were placed on the waiting list. The number of patients continued to increase. In 1980, there were 1,047 patients receiving treatment and 300 on the waiting list. In 1985, 2,581 patients underwent treatment and 259 were on the waiting list. Although the import of phGH gradually increased, it was not sufficient to meet the growing demand at the time, and 200–300 patients were constantly on the waiting list (16). During this period, the common clinical practice was to prioritize the treatment of older patients because of shorter treatment durations. Moreover, phGH supplied to one patient was often used to treat two patients, or a small amount of anabolic steroid was used concomitantly. Height restrictions to the treatment were also applied. Treatment was terminated once the height limit was exceeded (boys: 160 cm; girls: 150 cm). The height restriction was changed to 165 cm for boys and 152 cm for girls in 1986, but this was subsequently eliminated in 1992 (16).

The collection of human cadaver pituitaries has

limitations. Japan was criticized by supplier countries for “relying on the import of phGH (purchasing with money) instead of trying to procure pituitaries that were essential for phGH extraction for government-approved treatment within Japan”. In response, the FGS was founded in 1977 to collect pituitaries within Japan. The FGS established a pituitary bank and collected 31,786 pituitaries between 1978 and 1985. These were sent to Kabi Vitrum and Nordisk for the production of phGH preparations. In 1977, phGH preparations were approved and imported as Human Growth Hormone Nordisk® (Nordisk) and sold by Yamanouchi Pharmaceutical. Asellacrine® was imported from Calbiochem in the US and sold by Sumitomo Chemicals in 1978; Corpormon® was imported from the then Soviet Union and sold by Nikken Chemical in 1979; and Gorm® was imported from Serono in Switzerland and sold by Japan Chemical Research in 1985 (Fig. 1).

In 1974, the Maternal and Child Health Division of the MHW launched the Grant-in-Aid Program for Chronic Diseases in Childhood, which included pituitary dwarfism (later renamed GHD). As a result, high-cost phGH treatment became affordable with the help of insurance and subsidies from the project. This contributed to the increased use of hGH treatment. This system was enacted in 2005 in conjunction with the revision of the Child Welfare Act. After subsequent reviews, a Medical Aid Program for Chronic Pediatric Diseases of Specified Categories was established in 2015.

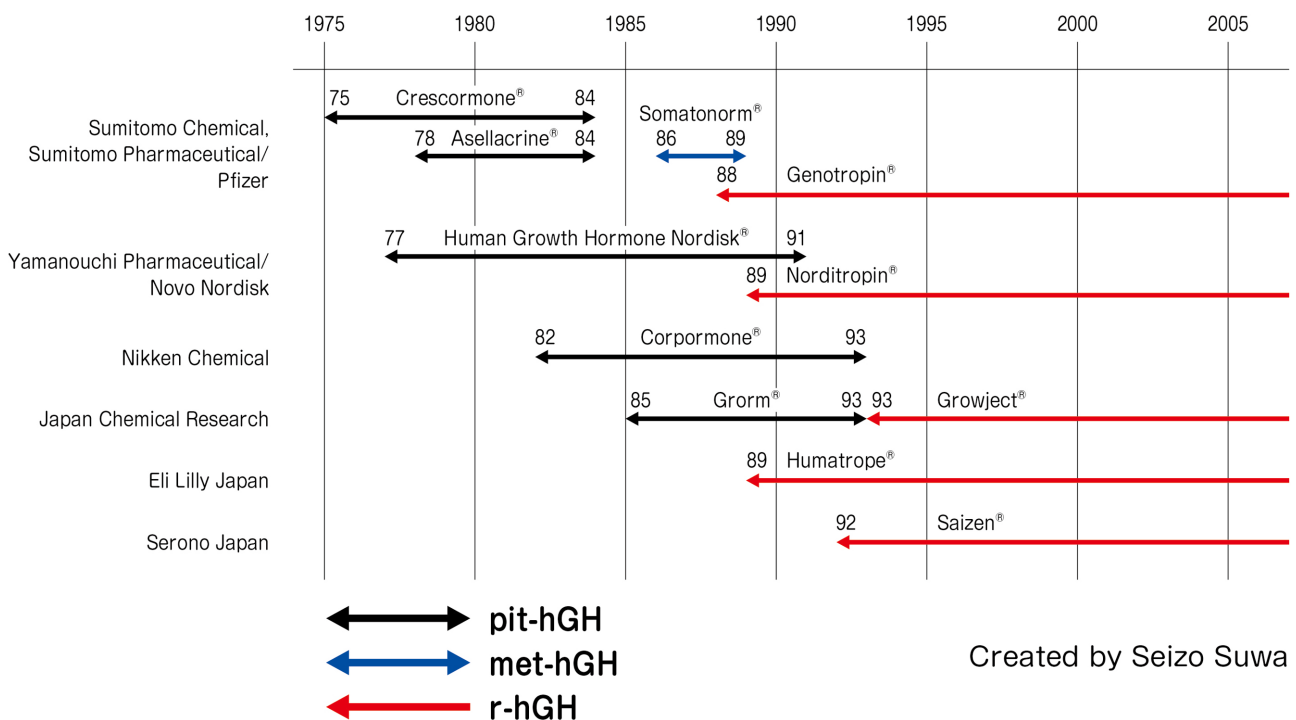


Fig. 1. Transitions in growth hormone preparations.

phGH Preparations and Creutzfeldt–Jakob Disease (CJD)

CJD is an infectious disease caused by a pathogen known as a prion. It triggers progressive spongiform encephalopathy, which leads to death within 1–2 yr. In 1985, multiple cases of CJD were reported in the US and United Kingdom (UK) in patients treated with phGH (17–19). It was thought that a large number of pituitary glands collected for hGH extraction might have been accidentally contaminated by the pituitary gland of someone infected with CJD, thereby causing the disease to develop in patients who used the batch. The European Society for Pediatric Endocrinology and Lawson Wilkins Pediatric Endocrine Society (the US Pediatric Endocrine Society) issued an advisory urging the discontinuation of phGH. As the US was already using Somatonorm®, a methionyl hGH (mhGH, hGH containing methionine added by genetic engineering), phGH was removed from the market.

In Japan, the FGS found that patients who developed CJD were limited to those treated with phGH extracted using the Wilhelmi method by the National Pituitary Agency in the US and Medical Research Council Working Group (University of Cambridge) in the UK, and an unknown method by the Pasteur Institute in France. As there was no incidence of CJD in patients treated with commercially available phGH preparations, phGH was not discontinued immediately. In 1986, Sumitomo Pharmaceuticals began importing and selling mhGH in Japan. One drawback of using Somatonorm® was that antibody production tended to increase over a long period due to an extra methionine molecule attached to the naturally occurring hGH, which reduced its growth-promoting effects in a few cases (20, 21). In 1988, Sumitomo Pharmaceuticals released Genotropin®, a bio-identical recombinant hGH (rhGH) that did not include an extra methionine molecule. Since then, other rhGHs have been launched. In 1989, Humatrope® was released by Eli Lilly Japan, followed by Norditropin® by Yamanouchi Pharmaceutical. Soon after, Saizen® by Sereno Japan in 1992 and Growject® by Japan Chemical Research in 1993 were introduced. As a result, phGH gradually disappeared from the market (Fig. 1).

The FGS's pituitary bank was permanently closed in 1986, the year when mhGH Somatonorm® was approved.

By 2003, the number of deaths from phGH-related CJD had reached 89 in France, 41 in the UK, and 23 in the US (22). Till date, there have been no reports of CJD caused by phGH marketed in Japan, including those used for investigative purposes.

FGS Activities

1) The GH Treatment Eligibility Assessment Committee

As mentioned earlier, the FGS was founded in 1977 to collect pituitary glands; however, the foundation had also engaged in many other activities and played a pivotal role in promoting GH treatment in Japan. The research group on pituitary dwarfism treatment was transferred to the FGS upon its establishment. The group was later reorganized as the GH Treatment Eligibility Assessment Committee in 1986 and has continued to carry out eligibility assessments till date. In the era of phGH, eligibility assessments were performed to ensure a fair distribution of the limited supply. After sufficient supplies of mhGH and rhGH became available, the purpose of the committee shifted to the provision of second opinions about diagnoses and appropriate treatment.

In 1993, the Maternal and Child Health Division of the MHW issued a public notification for the eligibility certification of the FGS to be included when applying for public funds for specific pediatric chronic diseases. Although the FGS followed the “Diagnostic Handbook” published by the MHW research group on hypothalamic–pituitary disorders as a basis for assessing eligibility, it used its unique scoring system based on reported findings (23). The scoring system included not only the results of GH provocation tests, but also reference findings such as perinatal problems, physiological GH secretion, IGF-I, and bone age in the diagnostic procedure. The scoring system could make a judgment about suspicious cases of GHD. Consequently, the system increased the eligibility rate, which raised the number of patients with GHDs. In 1997, eligibility certification was deemed unnecessary. Organizations for eligibility assessment were created by local governments across the country. Additionally, the eligibility for public subsidies became stricter, requiring a height SD score of ≤ -2.5 SD and IGF-I concentration limit.

Currently, the criteria adopted by the FGS are the same, as certain GHD with a height SD score of ≤ -2.0 SDs in the “Diagnostic Handbook” and suspicious GHD are not eligible for GH treatment.

The applications submitted to the FGS for eligibility assessment have formed the largest database of hGH treatments in Japan. This database has contributed to the development of hGH treatment in the country (24–29). More than 40 articles have been published till date, including reports on adult height data after long-term hGH treatment in Japan (24, 25), incidence of GHD in Japan (26), epidemiological data on the incidence of leukemia in patients treated in Japan (27), and the standardization of GH measurements (28–30).

2) Adult heights of GH-treated GHD [Fig. 2(a) and 2(b)]

The first adult heights of GH-treated GHD in Japan were reported by Hibi *et al.* from the FGS database in 1989 (24). Their mean adult heights in patients with isolated GHD (IGHD) and multiple pituitary hormone deficiency (MPHD) were 151.8 cm and 163.7 cm in boys, respectively, and 141.4 cm and 151.0 cm in girls, respectively.

Tanaka compared between the adult heights of patients with GHD treated with phGH and rhGH after 1986 (26). Their adult heights of IGHD were

and 160.5 cm among boys treated with phGH and rhGH, respectively, and 145.3 cm and 147.8 cm among girls treated with phGH and rhGH, respectively; their adult heights of MPHD were 162.4 cm and 161.4 cm among boys treated with phGH and rhGH, respectively, and 148.3 cm and 147.2 cm among girls treated with phGH and rhGH, respectively (25). The improvements in the adult heights of patients with rhGH-treated IGHD were due to the greater height SD scores at the start of GH treatment, as the improvements in the height SD scores from the start of GH treatment until adult heights were achieved were the smallest in rhGH-treated patients.

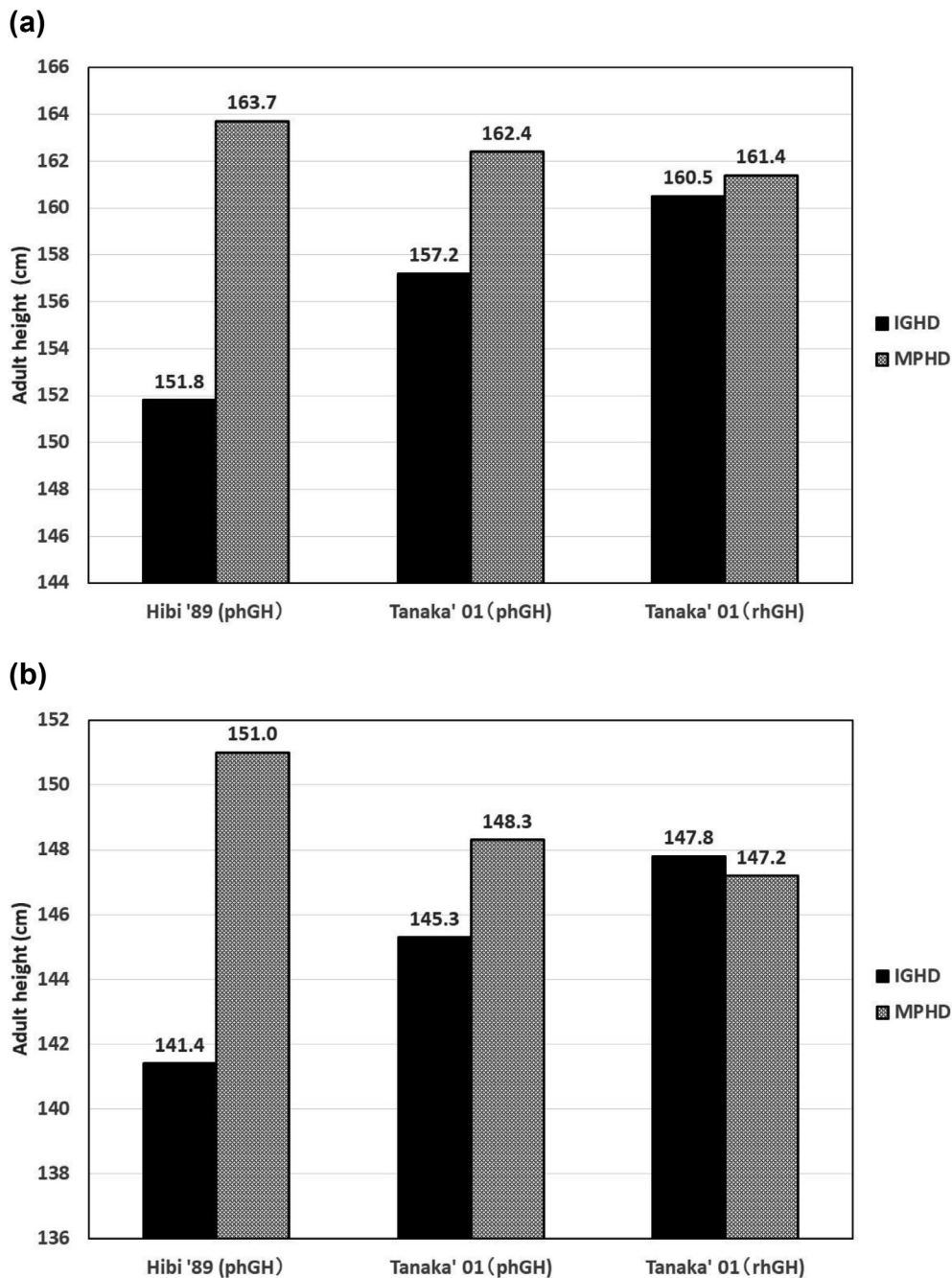


Fig. 2. (a) Comparison of adult heights after GH treatment between boys treated with phGH and rhGH. (b) Comparison of adult heights after GH treatment between girls treated with phGH and rhGH.

3) Standardization of GH measurements

The diagnosis of GHD was ultimately determined by the peak GH levels recorded by the GH stimulation tests. In 1991, there were six different measurement kits available, and the value for the same sample could differ by as much as two-fold across the kits. As the same peak GH cut-off was used as a diagnostic criterion, a different diagnosis based on the same sample may occur, depending on which kit was used. The FGS established an evaluation committee on GH-associated factors, led by Dr. Toshiaki Tanaka of the National Children's Hospital, to measure a large number of samples annually using all the kits. The committee created a conversion formula for each kit using the mean values of the kits by adopting the mean values of two RIA methods that were originally used. After the RIA methods were no longer used, the mean values of all the kits were used to correct the diagnostic discrepancies across the kits (28, 29). In this process, a standard solution prepared from rhGH was compared with that in each kit, and the measured values were found to be similar across all the kits. The standard solution included in each kit was prepared from phGH, and its titer was different across the kits, which were found to be the cause of the variabilities in the measured values. The committee then requested the manufacturer of each kit to use rhGH for the standard solution, to which they complied. Therefore, the conversion formula for each kit was eliminated in 2004. However, due to the difference in titers between the phGH standard solution previously used and rhGH, the peak GH cut-off for diagnosis was reduced from 10 to 6 ng/mL (28).

This method has been successfully used for some time. However, with the discontinuation of kits that use radioactive iodine and emergence of new kits in the market, variabilities in the measured values have resurfaced. Therefore, a conversion formula has been used for one kit since 2017 (30).

In the US and Europe, such standardization of measurements has not been successful, and there is no evidence as to whether all GHD cases are diagnosed in the same manner. Today, the FGS continues to conduct this activity to ensure the accuracy and fairness of the diagnosis of GHD in Japan.

4) GH treatment and leukemia

In 1988, Japan reported the onset of acute leukemia in children receiving hGH (31). This raised concerns about a possible link between the disease and hGH treatment. The news was published in newspapers, prompting some patients to discontinue treatment. To investigate this issue, the FGS established a research committee on leukemia led by Dr. Shaw Watanabe, who was the Director of the Epidemiology Division at the National Cancer Center. Stanke reported that among 31 patients with leukemia globally, which included

10 patients from Japan, there was no definite higher incidence in patients without a strong additional risk (32). The research committee on leukemia established by the FGS reported 14 cases of leukemia and one case of malignant histiocytosis in 1997. Dr. Yoshikazu Nishi performed detailed analyses of these 15 cases and conducted an epidemiological investigation of the risks using the FGS database. He reported the findings in the *Journal of Clinical Endocrinology and Metabolism* in 1999 (27). He concluded that the incidence of leukemia in patients treated with hGH was not different from that in healthy children, except for the high-risk group comprising patients with Fanconi anemia and those who had received radiotherapy or chemotherapy in the past. Thus, the speculation regarding leukemia and GH treatment was resolved.

Changes in the Diagnostic Criteria

The Study Group on Pituitary Dysfunction was launched in 1973 (later renamed The Study Group on Hypothalamic–Pituitary Dysfunction), and the group created the diagnostic criteria as the “Diagnostic Handbook: Pituitary Dwarfism”. However, the contents gradually changed over time (Tables 1 and 2).

One notable change was that the diagnostic name was altered to GHD. This change was made because the condition is not necessarily caused by the pituitary gland alone, the term dwarfism is considered discriminatory, and the revised International Classification of Diseases now uses the term “short stature” instead of “dwarfism”.

Some of the other changes included the alteration of the height SD score for diagnosis to -2.0 SD; the cut-off of the peak GH response to stimulation tests, which was previously increased from 7 to 10 ng/mL according to changes in the global diagnostic criteria, was reduced to 6 ng/mL based on the standardization of the GH measurement kits described above (28).

Intracranial organic disease and other pituitary hormone deficiencies were added to the main symptoms in 1999, according to the consensus meeting on the “Diagnosis and Treatment of Growth Hormone Deficiency in Childhood and Adolescence” held by the Growth Hormone Research Society in 1998.

The recent diagnostic criteria revised in 2018 are described briefly below:

I. Main symptoms

1. Height SD score of ≤ -2.0 SD or height velocity SD score of ≤ -1.5 SD for two consecutive years (one yr in the case of intracranial organic disease or other pituitary hormone deficiencies).
2. Symptomatic hypoglycemia due to suspected GHD in infants.
3. Intracranial organic disease or other pituitary hormone deficiencies.

II. GH provocation tests

Peak GH levels of ≤ 6 ng/mL in GH provocation tests among insulin, glucagon, arginine, clonidine, and L-DOPA loading (≤ 15 ng/mL in GHRP-2 test).

Table 1. Diagnostic Handbook made by the research group of the Ministry of Health and Welfare on hypothalamic–pituitary disorders

Revised Year	Disease	Main Symptoms
1975	Pituitary dwarfism	Height SDS ≤ -3.0 SD (≤ -2.5 SD in patients aged < 10 yr) Growth velocity ≤ 3 cm/yr
1984	Pituitary dwarfism	Height SDS ≤ -2.5 SD (≤ -2.0 SD in patients aged < 10 yr) Growth velocity $\leq 70\%$ for 2 yr
1987	Pituitary short stature	Height SDS ≤ -2.0 SD Growth velocity $\leq 70\%$ for 2 yr
1990	Pituitary short stature	Height SDS ≤ -2.0 SD Growth velocity ≤ -1.5 SD for 2 yr
1993	GHD	Height SDS ≤ -2.0 SD Growth velocity ≤ -1.5 SD for 2 yr Symptomatic hypoglycemia during infancy
1999	GHD	Height SDS ≤ -2.0 SD Growth velocity ≤ -1.5 SD for 2 yr Symptomatic hypoglycemia during infancy Intracranial organic disease/the other pituitary hormone deficiency

GHD, GH deficiency; SD, standard deviation; SDS, standard deviation score.

Table 2. Diagnostic Handbook made by the research group of the Ministry of Health and Welfare on hypothalamic–pituitary disorders

Revised Year	Peak GH	Classification
1975	≤ 5 ng/mL in all tests	
1984	≤ 7 ng/mL in 2 or more tests	
1993	≤ 10 ng/mL in 2 or more tests	Complete: ≤ 5 ng/mL in all tests Incomplete: Other than complete
1999	≤ 10 ng/mL in 2 or more tests	Severe: ≤ 5 ng/mL in all tests Moderate: Other than severe
2004	≤ 6 ng/mL in 2 or more tests	Severe: ≤ 3 ng/mL in all tests Moderate: Other than severe
2007	≤ 6 ng/mL in 2 or more tests (≤ 16 ng/mL in GHRP-2 test)	Severe: ≤ 3 ng/mL in all tests (GHRP-2 ≤ 10 ng/mL) Moderate: Maximum peak GH 3–6 ng/mL Mild: Other than severe and moderate

[Diagnostic criteria]

Certain GHD

1. Main symptom 1 and low GH peak in at least two provocation tests.
2. In a patient with main symptom 2 or main symptoms 1 and 3, the diagnosis can be made based on a low response to a single GH stimulation test.

Expansion of the Therapeutic Indications

Yamanouchi Pharmaceutical and Sumitomo Pharmaceuticals initiated a clinical trial on Turner syndrome at two doses: 0.5 and 1.0 U/kg/wk. Both companies found that the growth rate was higher among patients who received a dose of 1.0 U/kg/wk. In 1991, the MHW accepted Yamanouchi Pharmaceutical's report that "short stature in Turner syndrome is due to GHD" and approved the use of Genotropin® and Norditropin® at the "therapeutic dose of 0.5 U/kg/wk for the treatment

of Turner syndrome associated with GHD". It took until 1999 that the internationally accepted dose of 1.0 U/kg/wk regardless of the presence of GHD was approved, i.e., when Growject® by Japan Chemical Research was approved.

In addition to Turner syndrome, the indications for rhGH treatment expanded to include other growth disorders involving normal GH secretion, including short stature in children with chronic renal failure and achondroplasia/hypochondroplasia in 1997, Prader–Willi syndrome in 2002, SGA-associated short stature in 2008, and Noonan syndrome in 2017 (**Fig. 3**). In 2006, hGH treatment was approved for the treatment of severe GHD in adults.

In the US and Europe, rhGH is indicated for the treatment of SHOX deficiency and idiopathic short stature in some countries. A clinical trial for SHOX deficiency is currently underway in Japan. Regarding idiopathic short stature, approval of rhGH is unlikely

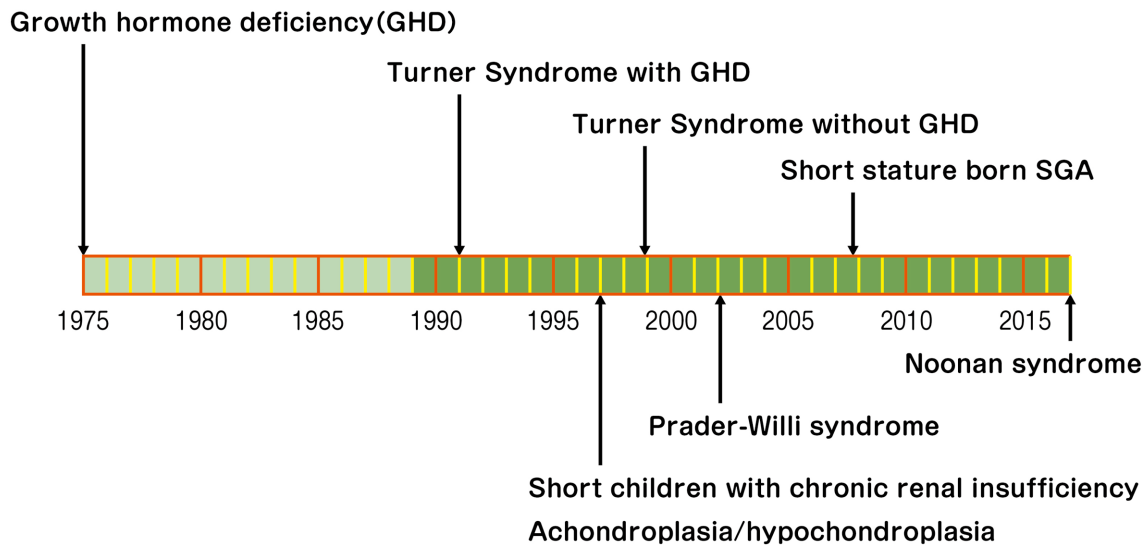


Fig. 3. GH treatment for growth disorders in Japan.

due to the government's policy to reduce the medical expenses covered by the NHI.

A once-weekly injectable hGH preparation has recently been developed. It has been approved for the treatment of adult GHD in Japan. For pediatric GHD, the product is currently being evaluated in a clinical trial, and the indication is likely to be approved in the future. Although its therapeutic effects are reported to be higher than those of currently available rhGH products, evaluation of the long-term safety of the

product is needed.

Conflicts of interests: The author has received consultation fees/honoraria from JCR Pharmaceuticals and has received honoraria from Pfizer.

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