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Review

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Growth hormone and Prader-Willi syndrome: experience and perspective

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Abstract

The initial report of Prader-Willi syndrome (PWS), published in 1956, described five major morbidities: short stature, hypotonia, obesity, hypogonadism, and cognitive delay. The clinical definition of PWS was fine-tuned over the next 3 decades; reported association with abnormalities in chromosome 15q in the 1980s led to the genetic definition in the 1990s. Human growth hormone (GH) was first purified in the 1950s, followed by increased therapeutic use of preparations purified from human pituitaries, which were emergently replaced by recombinant DNA-produced GH in 1985. Coincident developments in both fields led to trials of GH treatment for PWS and regulatory approval of GH treatment for PWS in 2000. As the only therapeutic agent with worldwide labeling for PWS, GH has shown efficacy for growth and hypotonia. Potential benefits for cognitive function and obesity have also been suggested, particularly with early treatment. A warning added in 2002 to the GH label for the PWS indication regarding use in severe obesity and severe respiratory impairment does not appear to be fully evidence-based; few other adverse effects have been observed. Delayed diagnosis and treatment of PWS continues to be a significant problem. The inclusion of PWS in newborn screening programs, a current area of research, would address the issue of late diagnosis, facilitating earlier initiation of GH treatment. Initial steps toward genetic therapy provide hope for a more complete medical treatment for this condition.

Keywords: Prader-Willi syndrome, growth hormone, obesity

INTRODUCTION

Recombinant human growth hormone or rhGH (somatropin and biosimilars) is the only medication with worldwide regulatory approval for the treatment of Prader-Willi syndrome (PWS). By chance, intention, and good fortune, my professional career as a pediatric endocrinologist has been closely associated with the clinical development of rhGH, particularly its application in PWS. In this review, I present an overview of PWS and GH through the lens of my personal experience.

GROWTH HORMONE: A BRIEF REVIEW

The human growth hormone (GH) gene, *GH1*, is located on chromosome 17q23.2 within a cluster of related genes, including those encoding placental GH and the placental lactogens - chorionic somatomammotropin hormones 1, 2, and 3[1]. These genes likely evolved via gene duplication, diverging from an ancestral gene that also gave rise to prolactin (*PRL*, chromosome 6p22.3). Endogenous GH production is restricted to pituitary somatotrophs due to tissue-specific gene expression. Its secretion is under positive and negative regulation by hypothalamic GH-releasing hormone and somatostatin, respectively. The *GH1* gene encodes two splice variants of GH, with approximate molecular weights of 21.5 and 20.0 kDa. Both isoforms contain two disulfide bonds, which are apparently not required for receptor binding or biological activity. In target tissues, dimeric GH acts via a type 1 cytokine transmembrane receptor (GHR). The extracellular portion of GHR circulates as the GH-binding protein.

As implied by its name, a primary function of GH is the stimulation of childhood skeletal growth, which is not a direct action. Instead, GH acts by directly and indirectly stimulating the production and secretion of growth factors and enzymes in the peripheral tissues. Regarding skeletal growth, GH stimulation of epiphyseal cartilage sulfation, a key event in bone growth, was found to be mediated by a cartilage sulfation factor, later renamed somatomedin-C, then once again renamed insulin-like growth factor-1 (IGF-I)[2]. The study of IGFs and their binding proteins evolved into major areas of research, independent of GH, that is beyond the scope of this manuscript[3,4].

Purification of GH from human pituitary glands (pGH) in the 1950s led to the development of methods for large-scale purification of GH and other hormones from human pituitary glands, facilitating clinical use[5]. In several countries, national agencies were established to collect and purify pituitary hormones. In addition, the development of radioimmunoassay methodology and a GH-specific assay facilitated direct assessment of GH levels and a realization that assessment of GH adequacy via peripheral blood sampling would require administration of a secretagogue due to the brief circulating half-life[6,7].

By 1962, the United States National Pituitary Agency (later renamed National Hormone and Pituitary Program, NHPP) was collecting an estimated 20,000 pituitary glands, primarily obtained from pathologists during autopsies; the amount skyrocketed as the program developed[8-10]. Partially purified hormone preparations were prepared in batches, bioassayed, and distributed for basic and clinical research, including clinical treatment. For clinical use, pGH was distributed under research protocols and was strictly limited to cases of severe organic childhood growth hormone deficiency (GHD), allocated in 6-month supplies, with the treatment regimen per patient depending on both hormone availability and treatment response. An estimated 365 pituitary glands were required to provide one year of treatment for a single patient. In 1978, the NHPP purification method was modified, increasing the purity of pGH from < 50% to approximately 95%. In addition to the research-grade product, commercial pGH also became available in the 1970s.

In 1973, a new technology for expressing synthetic DNA in E. coli cells was reported, and in 1976, Genentech was founded to take advantage of this technology, with initial proof of concept involving the production of somatostatin[11]. The first marketable product was recombinant human insulin (1978), which was sold to Eli Lilly and received marketing approval by the United States Food and Drug Administration (US FDA) in 1982[12]. In 1979, recombinant human GH with an N-terminal methionyl (met-rhGH, somatrem) was placed into clinical development.

When I started my postdoctoral fellowship in pediatric endocrinology with Dr. Raymond Hintz in 1983, Stanford University was a primary clinical study site for the Genentech clinical trials, and Dr. Hintz's laboratory was internationally recognized for studies of GH and IGFs, including the development of assays for somatomedin-C (IGF-I) and related proteins. Clinical trials of met-rhGH for the treatment of childhood GHD were in progress.

In 1984, a young adult patient who had been treated for childhood GHD through 1979 was evaluated in the Stanford pediatric endocrinology clinic; his mother noted that he had been walking abnormally. No specific abnormality was observed on the initial exam. However, the abnormal gait progressed along with rapid neurologic deterioration[13]. Based on clinical suspicion, Dr. Hintz referred the patient to the University of California San Francisco, a center for the study of "slow virus" disease. The patient died in November 1984; postmortem studies confirmed Creutzfeldt Jakob Disease (CJD), a condition known to be transmitted through ingestion or administration of brain tissue and thought to be due to an unidentified slow virus. Based on this and other cases, Dr. Hintz realized that the likely source of the infectious agent was pGH. In February 1985, he sent a letter of concern to the National Institutes of Health, NHPP, and FDA[13]. Following urgent review, the distribution of pGH was discontinued in the US in April 1985 and subsequently in other countries. CJD was eventually identified as a cause of more than 250 deaths in patients treated with pGH. Cases in the US were associated with the use of the pre-1978 pGH preparation. Recent reports suggest that pGH may have also transmitted amyloid β-protein, a possibly transmissible cause of sporadic Alzheimer's disease[14].

Although somatrem was still in clinical trials, the US FDA moved quickly to grant Genentech marketing approval for childhood GHD in October 1985 with the proviso that ongoing formal post-marketing surveillance safety studies be conducted[13,15]. This may have been one of the first formal regulatory requirements for post-marketing safety surveillance, contributing to the development of the now routine Phase 4 studies. Post-marketing surveillance studies for rhGH enrolled thousands of patients into registries and were incorporated into marketing programs providing honoraria and travel to hundreds of physicians who were enrolled as investigators. Although such practices were neither prohibited nor unusual in those days, the appearance of impropriety helped prompt the development of guidelines governing physician/industry interactions[16,17].

The abrupt transition from pGH to rhGH raised practical issues. The dosing of pGH had primarily been based on availability and was measured in bioassay-based units, due to significant activity loss during the purification process. Was the bioactivity of rhGH sufficiently predictable to allow dosing based on drug weight, and if so, how should the experience with unit-based dosing be converted to a weight-based regimen? Additionally, pGH was typically administered via intramuscular injection, with dose frequency dictated by its limited availability; could rhGH instead be given subcutaneously using the relatively new disposable insulin syringes, and what would be the optimal dose frequency?

In addition, concern persisted that GH itself might have been a direct or indirect cause of CJD, particularly because the cause of this condition was not yet fully defined. In 1982, Dr. Stanley Prusiner, a neurologist at the University of California San Francisco, proposed that CJD and similar conditions were protein-transmitted rather than caused by a slow virus - an idea initially met with skepticism but later confirmed. For this groundbreaking discovery of proteinaceous infectious particles, or prions, he was awarded the Nobel Prize in Medicine in 1997[18]. This work helped relieve the concern that GH was the cause of CJD.

The pricing and distribution of somatrem also raised concerns, particularly regarding the potential for indiscriminate use. Governmental agencies had previously distributed pGH to patients without charge, and the brief experience with commercial marketing of pGH provided limited guidance. In the US, initial attempts to limit distribution to hospital pharmacies encountered difficulties and agreement was made that distribution would be via a home healthcare organization. The onerous process of documenting the need for pGH treatment was revised for rhGH and remains in place in the US to this day.

Despite regulated distribution, the abuse of human and animal growth hormone preparations became prevalent through underground marketing, particularly among bodybuilders and other individuals. This illicit use was driven by data showing that, beyond promoting childhood skeletal growth, GH also had positive effects on nitrogen balance and muscle development. In 1990, the US Congress passed the Anabolic Steroids Act, an amendment to the Controlled Substances Act (1970), adding restrictions on the distribution and use of anabolic steroids and, separately, GH, although GH is not classified as a steroid[19].

The availability of rhGH led to US FDA marketing approvals for the treatment of several conditions involving childhood growth failure, including Turner syndrome (1996), chronic renal failure (1997), PWS (2000), small for gestational age without catch-up growth (2001), idiopathic short stature (2003), SHOX DNA defect (2008), and Noonan syndrome (2007). Additional approved indications included adult human immunodeficiency-associated wasting and adult GHD (both in 1998), as well as short bowel syndrome (2003). Many of these indications were also approved by regulatory agencies in other countries.

As summarized in this brief review, GH treatment holds a special place in the history of medical science, playing important roles in the development of recombinant DNA technology, regulatory requirements for drug development, and medical ethics.

PWS: A BRIEF AND SELECTIVE REVIEW

In 1956, three physicians from the University of Zurich - Andrea Prader, Alexis Labhart, and Heinrich Willi - published a half-page report describing a condition observed in nine individuals. The reported features included Adipositas (obesity), Kleinwuchs (small stature), Kryptorchismus (cryptorchidism), Oligophrenie (intellectual disability), and Nach Myatonierartigem Zustand Im Neugeborenenalter (following a myotonia-like status in infancy; described in the text as neonatal hypotonia that gradually improved over time)[20]. Delayed or incomplete puberty was also noted. Although the same condition may have been described earlier by Langdon Down in 1887 and in 17th-century descriptions of Eugenia Martinez Vallejo (*aka* La Monstrua)[21], the brief 1956 manuscript was the first concise yet remarkably comprehensive description of what is now recognized as Prader-Willi syndrome[22].

Additional cases and further delineation of the clinical syndrome were enhanced by the work of several groups, including Dr. Hans Zellweger and his colleagues at the University of Iowa, where a patient registry was established[23]. In 1975, the Prader-Willi Syndrome Association (PWSA) was founded by Gene and Fausta Deterling, parents of a newborn with PWS, supported by Dr. Vanja Holm at the University of

Washington, a pioneer in PWS research. PWSA, its national affiliates and other similar organizations around the world have been a major driving force for medical research, clinical care, and psychosocial management of individuals with PWS.

In the 1970s, reports of chromosome 15 abnormalities were reported in a few cases of clinically diagnosed PWS. A seminal manuscript in 1981 by David Ledbetter *et al.* proposed the deletion of chromosome 15q11-13 as a cause for PWS[24,25]. In 1983, Butler and Palmer described this deletion as specific to the paternal copy of chromosome 15. However, a significant proportion of clinical cases did not have this deletion, which continued to foster doubt regarding the genetic association. The missing piece was solved in 1989 with the report of maternal uniparental disomy 15 in most of the remaining cases[26].

Despite this progress, the recognition of PWS as a unique condition was still regarded with some doubt. As a medical student, I can recall being informed that PWS was simply a condition of children with mental retardation and short stature, with food-seeking behavior leading to obesity. Even with the discovery of the associated genetic abnormality, the limited availability of genetic testing perpetuated misconceptions. Clinical diagnostic criteria for PWS published in 1993 included "Deletion 5q11-13 on high resolution (> 650 bands) or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy" as one of 8 major criteria rather than as a requirement for the diagnosis[27].

In 1990, I partnered with geneticist Dr. Frank Greenberg and gastroenterologist Dr. William Klish to start a multidisciplinary PWS clinic at Texas Children's Hospital, Baylor College of Medicine, Houston, Texas. As a first step, a decision was made that all patients enrolled in the PWS clinic were required to have a characteristic chromosome 15 abnormality, usually via testing in Dr. David Ledbetter's laboratory at Baylor. Somewhat to our surprise, a large proportion of referred patients did not have a chromosome 15 abnormality and had been clinically misdiagnosed. The Texas Children's Hospital PWS Clinic continues to serve as a model for multidisciplinary management under the leadership of Dr. Ann Scheimann.

PWS is now defined by the lack of expression of paternally expressed genes located at 15q11-13, resulting from deletion, uniparental disomy, or rarely an imprinting defect. Similar clinical characteristics are described for other genetic conditions, most notably Schaaf-Yang syndrome, a condition associated with mutation of *MAGEL2*, one of the imprinted genes located in the PWS region of 15q11-13[28].

Acceptance of a genetic criterion for PWS followed by studies in patients with genetic confirmation of diagnosis increased our appreciation for the initial clinical syndrome description in 1956, which astutely recognized the five major morbidities of PWS[22,29]:

(1) Severe neonatal hypotonia, which, unlike many other congenital hypotonic conditions, improves (but does not normalize) during late infancy and early childhood. The hypotonia starts *in utero* with decreased fetal movement. Feeding problems and delayed neuromotor development are important features of neonatal/infantile hypotonia. Although muscle function improves, hypotonia persists throughout the lifespan. The hypotonia is associated with a lack of muscle mass with normal muscle fibers[30], and unlike in usual obesity, the deficient muscle mass persists even with excessive weight gain[31].

(2) Short stature. A fall in height percentiles (i.e., decreased height velocity) is typically noted after 18 to 24 months. Concurrently, levels of IGF-I fall below the reference range, implying a deficiency of GH secretion[32]. However, GH deficiency is not always found in standard testing and the pathogenesis of the GH/IGF axis deficiency has not been fully defined.

(3) Obesity, as defined by excess body fat, e.g., relative to lean mass. This should not be confused with weight or body mass, which is the total of fat and lean mass. PWS infants with low weight have excess fat to lean mass[33]. Individuals with PWS who have excessive weight gain acquire an excessive proportion of fat mass compared to non-PWS individuals[31]. The excessive gain in body fat coupled with minimal gain in lean mass is accompanied by an insatiable hunger similar to starvation. The hyperphagia and changes in body compartments are unlike those in non-PWS individuals, in whom eating is typically satiable and both lean and fat mass increase with weight gain, as previously reviewed[34].

(4) Hypogonadism, which may manifest as cryptorchidism and micropenis in males, delayed and incomplete puberty in both males and females, including delayed or absent menarche in females. Although some males may have primary hypogonadism related to cryptorchidism, the hypogonadism of PWS primarily involves a central dysregulation of gonadotropin secretion[29].

(5) Intellectual disability, Cognitive delay. A primary feature of PWS is cognitive delay, which, along with hypotonia, contributes to delayed speech development. Cognitive delay is also considered to be a major contributor to behavioral abnormalities in children and adults with PWS.

PWS MEETS GH

In 1984, Dr. Delfin Beltran, an anesthesiologist and head of the Stanford Medical Intensive Care Unit, brought a young family member to the endocrinology clinic who had been clinically diagnosed with PWS when she was 3 years old[35]. She had been placed on a strict, very low-calorie diet, a standard treatment at that time. In addition to a strictly controlled weight, she had severe short stature. Dr. Beltran proposed that this was due to GH deficiency. At that time, we were conducting studies to validate IGF-I (somatomedin-C) as a marker of GH deficiency. To our surprise, the child had a very low IGF-I level and a near-absent GH response on stimulation testing. She was treated with pGH treatment and then transitioned to rhGH. This led to the investigation and GH treatment of three additional children with PWS, with results presented at the 2nd annual PWSA Scientific Conference in 1987 and published that year[36].

Preceding data and subsequent publications from other centers supported our findings of a GH/IGF system deficiency in childhood PWS and beneficial effects on height velocity and motor function during GH treatment. Particularly notable were the detailed reports from Dr. Moris Angulo[37] and Dr. Urs Eiholzer[38]. In 1999, a landmark randomized controlled study of GH treatment in childhood PWS was published, with Dr. Aaron Carrel as the principal investigator[39]. Results from that study were presented in a GH symposium held during the annual PWSA National Scientific meeting in 1999, and subsequent publications confirmed the continued benefit of treatment[40-43]. The following year, initial regulatory labeling for GH treatment of PWS was achieved by Pharmacia and Upjohn, a pharmaceutical company that merged with Pfizer in 2003.

In 2000, I was invited by Pharmacia and Upjohn to organize a US advisory board of endocrinologists for PWS[6]. I agreed on the condition that the board would be multidisciplinary instead of endocrinologist-only, including medical subspecialists in several fields and the director of PWSA, Janalee Heinemann. The US PWS Advisory Board undertook several projects to educate healthcare professionals and caretakers regarding the diagnosis and management of PWS. Among the achievements were an educational video and the publication of Management of Prader-Willi Syndrome, 3rd edition (2006). Collaboration with the International PWS Advisory Board, organized and led by Dr. Urs Eiholzer, resulted in international consensus guidelines for the medical management of PWS, which included GH treatment.

Since then, GH has gained worldwide acceptance as a standard-of-care treatment for PWS, with a generally favorable benefit-to-risk ratio. However, GH treatment does not address all five major morbidities of PWS, and its efficacy is clearly dependent on age at the start of treatment. Furthermore, many individuals with PWS do not receive GH treatment or have delayed treatment due to safety concerns that may not be fully justified.

EFFICACY OF GH TREATMENT ON THE PRIMARY MORBIDITIES

A comprehensive review of GH efficacy in PWS is beyond the scope of this manuscript. Selected highlights are presented; the reader is referred to other sources for more detailed information[44,45].

Short stature

Among the five major PWS morbidities, short stature is arguably the least medically concerning. Nevertheless, it provided the initial rationale for investigating GH status and treatment, which ultimately drew scientific and medical attention to the syndrome. Moreover, depending on the degree of the height deficit, severe short stature can pose a significant functional limitation.

Several population-based growth charts for non-GH treatment children with PWS have been compiled by Dr. Merlin Butler[46]. Regional variability is evident, perhaps related to the growth characteristics of the reference population (although this has not been specifically studied), and dependence on parental heights has been suggested. However, a general characteristic is that the 90 to 95th percentile for adult HT in PWS is at approximately the 50th percentile for the reference population; the 3rd to 5th percentile for PWS is ~ 130 to 140 cm.

Decreased height velocity in PWS typically begins after early infancy, coincident with the tendency toward excessive weight gain (although obesity *per se* is congenital). The decreased height velocity is associated with decreased IGF-I levels. GH levels are usually low on stimulation testing. However, as in non-PWS populations, assessment of GH adequacy may vary with the test conditions, GH secretagogue(s) used for the procedure, and criteria used for defining an adequate response[6]. Hypothalamic dysfunction is usually invoked as the cause for the apparent deficiency in the GH/IGF axis, although data are not conclusive; no structural abnormalities in the hypothalamus or pituitary gland have been identified. IGF-I levels rise with GH treatment, which rules out an intrinsic defect in IGF-I synthesis. A peripheral signaling abnormality, perhaps related to low muscle mass, leading to deficient GH secretion has been proposed; however, supportive data for this hypothesis are also lacking[44,47].

Although the causative mechanisms have not been defined, there is no question that rhGH treatment of children with PWS has a positive effect on improving growth rate and adult height[45,48], with earlier initiation of treatment having a more pronounced effect on height[49,50]. In childhood, height is a convenient measure of treatment efficacy.

In the US, the labeled PWS-specific treatment indication for GH is limited to childhood growth failure, although adults with PWS clearly benefit from treatment[51]. Depending on test conditions and clinical criteria, adults with PWS may have low GH and/or IGF-I levels[44,52]. meeting criteria for the adult GH deficiency indication, with treatment monitoring based on normalization of IGF-I levels; continuation of GH treatment may be difficult or impossible for those who do not meet adult GHD criteria. This may be less of an issue in non-US regions where body composition is included in the labeled indication.

Hypotonia

Severe hypotonia in PWS is a universal feature of the condition and contributes to several medical complications. The hypotonia, which begins *in utero* with decreased fetal movement, is due to an absolute decrease in muscle mass. The hypotonia contributes to feeding issues in infants, with many infants initially requiring intravenous nutrition followed by enteric feedings via nasogastric or gastrostomy tube. Delayed neuromotor development is also observed, with milestones delayed by 6 or more months, and the pharyngeal hypotonia contributes to speech delay (which is also conditioned by the cognitive impairment). Over time, the existing muscle gains strength, a process benefited by physical therapy. Virtually all children with PWS are ambulatory by 2 to 3 years old. However, the hypotonia continues to adversely affect fine and gross motor function, breathing, and respiration. Respiratory or cardiorespiratory failure is the most commonly identified cause of premature mortality in PWS. Congenital hypotonia may contribute to the frequent occurrences of congenital or early-onset scoliosis and hip dysplasia.

The cause of the low muscle mass and hypotonia have not been elucidated. No abnormalities in the muscle fibers themselves have been identified[30], nor have any intrinsic abnormalities in muscle metabolism been found. As mentioned above, unlike other congenital myopathies, there is no degeneration of the existing muscle tissue, and muscle function tends to improve with age, although it is still grossly deficient.

In my experience, alleviation of hypotonia was the most dramatic unexpected observation during initial trials of GH treatment in PWS and is the major physical benefit of this treatment. Infants with PWS who received GH treatment may have a shorter duration of feeding difficulties and an improved rate of neuromotor development. In children with PWS, GH treatment improves breathing and respiration, and muscle strength and function. The beneficial effects of GH treatment on muscles have also been demonstrated in adults with PWS. In my experience, hypotonia recurs within months of stopping GH treatment in infants, children, and adults with PWS, emphasizing the importance of uninterrupted treatment.

Obesity

In medical terminology, obesity refers to excessive body fat, either absolute or as a proportion of total body mass; the latter comprises fat and lean (muscle plus bone) mass in a clinical 3-compartment model of body composition. This definition is often modified to refer specifically to excess fat that adversely affects health. A quantitative definition of excessive fat is lacking in both PWS and non-PWS populations, and the specific level of obesity that adversely affects health is similarly undefined.

In the 1970s, the US Centers for Disease Control (CDC) adopted body mass index (BMI) as a measure of population-based obesity, with BMI calculated as [mass(kg)/height(m)^2][53] and BMI-based definitions of obesity in adult and pediatric populations were established. However, recognizing the inter-individual variability in body composition, the CDC has consistently cautioned against using BMI to diagnose obesity in individual patients. Current information on the CDC website includes this statement: "BMI does not distinguish between fat, muscle, and bone mass. These all influence a person's weight. BMI does not indicate what types of fat people have. BMI also does not indicate where in the body that people carry fat." (https://www.cdc.gov/bmi/about/index.html#cdc_health_safety_special_topic_how-bmi-for-screening.) Nonetheless, BMI has become an entrenched clinical tool for diagnosis and monitoring of obesity in individuals, often superseding or replacing actual examination evidence of excessive body fat or consideration of clinically relevant fat distribution. This inappropriate use of BMI for clinical diagnosis of obesity has been repeatedly called into question[54].

In non-PWS populations and, to some extent, in an average non-PWS individual, the use of BMI to reflect fatness bears some validity based on evidence showing that as mass increases, fat and non-fat mass increase concurrently in a non-parallel relationship. On the higher end of total mass (body weight), fat increases faster than lean mass, while on the lower end, fat decreases faster than lean mass; this relationship has been termed the Companionship of Fat and Lean[55].

In detailed studies, Forbes *et al.* demonstrated superimposable lean *vs.* fat mass ratios across a range of body mass in normal physiology and in several disease populations[56]. With weight loss due to overall calorie reduction, fat and lean mass decrease; the loss of lean mass could be alleviated by an increased proportion of protein intake. In these studies, individuals with PWS were identified as the only group to show a different proportion of lean vs. fat mass; at a given level of total mass, individuals with PWS had a notably lower proportion of lean mass[31]. As in non-PWS populations, lean mass increases with total mass (weight) but proportionately less than observed in other populations. Subsequent studies confirmed this disproportion, including in underweight infants with PWS and in PWS patients with high BMI[33,57,58]. Therefore, individuals with PWS can be considered obese at any given level of total body mass.

Interestingly, although the proportion and absolute amount of body fat are high, there are no data indicating increased risk in PWS for typical obesity-related morbidities. Premature adrenarche and precocious puberty are known to occur with increased frequency in non-PWS children; in my experience, these conditions are uncommon in PWS, although this may be discordant with some published data[59]. Similarly, type 2 diabetes mellitus and atherosclerotic heart disease may occur less frequently than might be expected in PWS.

Despite the lack of convincing evidence for metabolic and cardiovascular complications of obesity, the excessive body fat resulting in excessive total body mass coupled with decreased muscle mass and function logically contribute to other morbidity in PWS. For instance, breathing and respiration are adversely affected, leading to increased severity of respiratory illnesses and contributing to premature mortality. In my experience, individuals with PWS and an absolute excess in fat mass have a high risk of developing ventilator dependence if intubated during respiratory illness.

How does GH treatment affect body fatness in PWS? First, due to increased muscle mass, body fat as a proportion of total mass is reduced. Published data and anecdotal experience indicate that excessive weight gain and the appearance of excessive body fat can be prevented particularly if GH treatment is initiated at an early age[37,38,60].

Although not included in my list of major morbidities, hyperphagia is a significant concern in PWS, contributing to concern about excessive weight gain. Based on my personal observations, the hyperphagic behavior in PWS resembles that observed in starvation; affected children often exhibit uncontrollable foraging behavior, which differs markedly from the overeating observed in non-PWS children. The cause of this behavior is unclear. Although a hypothalamic disorder is often cited, there is no evidence of an abnormality in orexigenic hormones or neurotransmitters. Another hypothesis is that there is a lack of peripheral signaling of satiety, perhaps related to gastric hypotonia[34].

Hypogonadism

Based on my clinical experience, GH treatment has minimal or no effect on genital development or gonadal function in PWS. However, detailed studies have not been published. In non-PWS populations, GH treatment may have effects on penile growth, testicular descent, and gonadal (ovarian and testicular)

function[61-63].

Cognitive delay

Many years ago, we observed accelerated growth of head size in infants with PWS during GH treatment. In some cases, the head growth raised concern for hydrocephalus; however, imaging studies did not reveal any pathology; the increased head growth was due to brain growth. These observations raised the possibility that accelerated brain growth with GH treatment starting in infancy could benefit cognitive delay. Published data support the beneficial effects of early GH treatment on neurodevelopment outcomes[64,65]. Beneficial effects on behavior have also been reported[66].

GH SAFETY IN PWS

As mentioned previously, regulatory approvals for rhGH starting in 1985 were accompanied by requirements for post-marketing surveillance[15]. The Genentech National Cooperative Growth Study (NCGS), established by Genentech (now a subsidiary of Roche), enrolled 65,205 patients between 1985 and 2010, ending with 240,951 patient-years[67]. The Kabi International Growth Study (KIGS), established by KabiVitrum (subsequently purchased by Kabi Pharmacia, then by Pharmacia & Upjohn, and eventually by Pfizer), enrolled 83,803 patients from 1987 to 2012, with 277, 264 patient-years[68]. Most of the patients in NCGS and KIGS were pediatric, with the largest proportion having a diagnosis of GH deficiency. A sub-study of KIGS, the Kabi International Metabolic Database (KIMS), enrolled 15,809 adults treated with rhGH, including approximately 84,000 patient-years of experience. Additional smaller surveillance databases were established by other companies[69].

Composite database analyses across all treatment indications demonstrate that rhGH treatment has a favorable risk-to-benefit ratio[67,70-72]. Most adverse events are assessed to be unrelated to the rhGH treatment. Exceptions may be transient intracranial hypertension and (particularly in adults) peripheral edema, both likely related to the acute effects of GH on salt and water retention. Slipped capital femoral epiphysis is often cited as an adverse effect, but its relatedness to the treatment is unclear. Initial diagnosis or exacerbation of scoliosis is also frequently reported; however, this also occurs in the general pediatric population and is related to vertebral growth.

The safety cohort for KIGS included 2,338 patients with PWS, of whom 511 were also enrolled in NCGS. Detailed analysis of the KIGS database revealed respiratory and musculoskeletal (e.g., scoliosis) as the most common adverse events in PWS patients, each occurring in < 2% of patients. These adverse events are not surprising given the already increased occurrence of respiratory impairment and scoliosis in non-GH treated PWS, both of which may be related, at least in part, to intrinsic hypotonia. PWS-specific analysis of the NCGS database has not been published. Similar safety findings have been reported in 4 smaller surveillance studies[69,73].

GH is known to decrease insulin sensitivity and rhGH treatment could increase the risk for type 2 (insulin-resistance-related) diabetes mellitus (T2DM). Anecdotal experience indicates that prediabetes and T2DM can occur in PWS patients, particularly those with uncontrolled weight gain and other evidence for insulin resistance, and a few cases of diabetes mellitus have been reported in the GH surveillance databases[69,73]. It is unclear whether rhGH treatment increases the risk for these conditions as compared to untreated PWS or a similar non-PWS population; however, in my experience, stopping or lowering the dose of rhGH coupled with dietary management results in improvement or resolution.

Early in the history of GH treatment of PWS, concerns were raised that behavior could be adversely affected and that the normalization of phenotype could be detrimental to behavioral treatment since the individuals would no longer appear to have PWS. However, neither concern has been validated, and as mentioned previously[66], at least one study has shown improved behavior with rhGH treatment.

In 2002, two deaths during GH treatment with PWS were reported, both young children who had recently started treatment[74]. These cases and three others identified by the Pediatric Endocrine Society raised concern that GH might contribute to mortality in PWS, leading to the placement of a warning on the rhGH label for PWS: "Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory failure." Although both conditions are common in PWS, the label does not provide any supportive evidence or clinical guidance for evaluation.

In 2006, I reviewed all deaths in individuals with PWS during GH treatment, which included 3 from KIGS, 3 from NCGS or reported to Genentech, 4 reported via pharmacovigilance, and 7 published cases[75]; 13 of these had been previously reported[76]. The 17 cases ranged in age from 0.7 to 15.8 years (mean ± SD, 7.0 ± 4.3 years), with durations of rGH treatment ranging from 2 weeks to 2.5 years (mean ± SD, 0.57 ±0.66 years), and had a high weight or BMI. Sixteen of the 17 cases with available rhGH dose information were prescribed doses between 0.10 and 0.33 mg/kg/week (mean ± SD, 0.18 ± 0.06 mg/kg/week), with 12 receiving doses below the labeled recommendation of 0.24 mg/kg/week and below doses reported in the literature, which range up to 0.35 kg/mg/week. Among the 9 cases with identified contributory factors, all involved respiratory illness. Comparison with available natural history data of PWS indicated that the GH-treated population likely had a lower mortality rate, with causes of mortality similar between treated and untreated groups. Also striking was that all cases had relatively short treatment durations, and most received potentially sub-therapeutic doses. These findings indicate that GH treatment is not associated with mortality in PWS, a conclusion supported by data from the French Registry for PWS[77]. In fact, the initial case report had remarked that "The boy reported here…thus died before the effects of GH therapy could manifest themselves."

A few additional deaths in PWS during GH treatment have been reported in the pharmacovigilance databases and in the literature. Most cases lack complete details, but the available information does not appear to counter the findings and conclusions in my 2006 review. Short duration of treatment is characteristic; few, if any, cases are reported with extended treatment duration or higher doses. In addition, no effect or improvement of sleep-disordered breathing and silent aspiration has been reported for infants with PWS during rhGH treatment[78,79]. which is consistent with previous studies demonstrating GH-related improvements in breathing and respiration[80,81]. Data from a matched cohort study including 360 individuals with PWS confirmed the intrinsic increased mortality rate in PWS and suggested that GH treatment might be associated with improved longevity[82].

Despite the lack of supportive data, the warning label remains. In my experience, this has led to an illogical hesitance to treat infants and young children with PWS, often based on polysomnography results, although GH is the only medical treatment that improves breathing and respiration in PWS.

FUTURE DIRECTIONS

GH treatment has provided significant benefits for individuals with PWS, with significantly greater efficacy if started in infancy. The importance of making the diagnosis of PWS in infancy, including genetic screening of hypotonic infants, was emphasized in 1987, even before the widespread availability of genetic testing and GH treatment[83]. This has been repeatedly re-emphasized in several subsequent publications,

including in the revised clinical diagnostic criteria in 2000[84]. However, despite these guidelines, many individuals with PWS are not diagnosed in infancy and are subjected to extensive diagnostic testing and treatments that may not have been necessary if the diagnosis had been assigned. In my personal experience in recent years, most cases of PWS are not diagnosed in the neonatal period and many remain undiagnosed until early to mid-childhood, missing a critical period for initiation of GH treatment.

Prenatal testing for PWS is complicated by a lack of definitive fetal phenotype or parental risk factors (except in very rare cases of relevant heritable genetic abnormality) and the limited ability of standard non-invasive prenatal testing (NIPT) to detect a suspicious fetal genotype. In addition, NIPT is usually only performed for pregnancies that are considered at high risk due to maternal age or other factors, with analysis focused on common aneuploidies of chromosomes 13, 18, or 21. A few cases of prenatal or abortion fetal diagnosis have been reported involving the detection of trisomy 15 on NIPT followed by invasive (e.g., amniocentesis, fetal tissue sampling) confirmatory testing[85].

The inclusion of PWS in newborn screening programs could be an effective means of addressing early recognition and treatment. However, the lack of a testable biomarker means that this would involve genetic testing, either as a standalone procedure or as part of testing for other disorders. The feasibility of using *SNRPN* methylation screening for the detection of PWS and Angelman syndrome has been recently described[86]. In addition, progress continues to be made regarding non-invasive prenatal testing for PWS[85,87]. Meanwhile, all healthcare providers involved with the care of neonates should be aware that unexplained hypotonia and poor suck are sufficient criteria for PWS testing, usually by *SNRPN* methylation analysis[84].

On March 27, 2025, Vykat XR (Soleno Therapeutics) was awarded marketing approval in the US for the treatment of hyperphagia in patients with PWS ≥ 4 years old, becoming the second drug product with specific labeling for the treatment of PWS. The efficacy of Vyakt XR was assessed in a double-blind, randomized, placebo-controlled study using a validated hyperphagia questionnaire[88-90]. Vykat XR is a long-acting choline salt of diazoxide, a drug used for the treatment of hypoglycemia due to congenital hyperinsulinism and islet cell tumors. Among other actions, diazoxide opens the beta cell K-ATP channel, which then decreases insulin secretion, the primary lipogenic and hypoglycemic hormone. Common adverse events of diazoxide use in the treatment of hypoglycemia include loss of appetite, nausea, gastrointestinal disorder, change in taste sensation, and hypertrichosis. Common adverse events during clinical trials of diazoxide choline included hyperglycemia, hypertrichosis, edema, and rash. Post-marketing experience, including clinical assessment of cost/benefit, will provide a better understanding of how Vykat XR can be included in the comprehensive care of patients with PWS.

A potential issue with weight loss therapy in individuals with PWS and other conditions, whether via diet alone or with drug therapy, is the obligate loss of muscle mass. This could be particularly detrimental in PWS, where there is an unusual deficiency of muscle mass[31]. During glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment of non-PWS obesity, approximately 30% of weight loss is attributable to lean mass[91]. Although not yet studied for diazoxide choline treatment, studies in rodents have shown acute inhibition of muscle protein synthesis with diazoxide-induced insulin deficiency[92]. Loss of lean mass can be partially countered by increased protein intake[93]. Of the commonly used weight management medications, metformin has been shown to preserve lean mass, an effect that may be augmented by resveratrol[94,95]. Growth hormone treatment has also been shown to conserve lean mass while also increasing lipolysis during calorie restriction[96]; studies in PWS have not been published.

In my opinion, the next major advance in PWS treatment will be gene therapy, perhaps via activation of the non-expressed paternal genes within the PWS locus[97], a technology that is still in the early stages of basic research.

CONCLUDING REMARKS

Concurrent progress in defining the genetic basis of PWS and the development of rhGH in the 1980s led to worldwide regulatory approval of rhGH treatment for PWS in 2000. rhGH treatment of PWS has well-characterized beneficial effects on growth, muscle mass and function, and breathing and respiration. Treatment efficacy is most significant if started in infancy. However, many cases continue to be late-diagnosed and a warning on the product label may further limit treatment.

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The author is the sole contributor to this manuscript.

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Conflicts of Interest

Phillip D.K. Lee, Guest Editor of the Special Issue "Prader-Willi Syndrome: Clinical, Genetic, and Endocrine Research" in the journal *Rare Diseases and Orphan Drugs*, also serves as an Associate Editor of the journal. He was not involved in any steps of the editorial process for this manuscript, including reviewer selection, manuscript handling, or decision making.

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