Opinion

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Beneficial Effects of Growth Hormone Treatment in Prader-Willi Syndrome

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Prader-Willi syndrome (PWS) is a genetic disorder that is considered, especially on child, to cause poor feeding, hypotonia, failure to thrive, developmental delay and hypogonadism which is known to affect between 1 in 10,000 and 30,000 people. The children with PWS are viewed as affected by growth hormone (GH) insufficiency, although the exact mechanisms of GH deficiency are not fully understood. However, the benefits of GH treatment in children with PWS are well established. Myers, et al. (2006), Grugni, et al. (2016) indicated its positive effects on linear growth, body composition, motor function, respiratory function and psychomotor development. Despite of its effectiveness and advantages had been well known and proven in many other studies, there is only one recombinant GH product that is approved for PWS in Korea, Genotropin®, till now. A phase III clinical study of GH treatment with Eutropin™, in 34 Korean PWS children is in progress, which is expected to have comparable effects and safety profile with the active control by assessing auxological changes such as height standard deviation score, body composition changes such as lean body mass and percent body fat, motor and cognitive development using Bayley scale, and safety profiles.

Keywords: Prader-Willi syndrome, Growth hormone, Clinical trial

Prader-Willi Syndrome (PWS) is genetic disorder with hypothalamic dysfunction, which was first described by Prader and Willi in 1956[1]. Hypothalamic dysfunction in PWS is thought to be caused by the loss or failure of imprinted gene expression within chromosome 15q11-q13 as a result of the paternal copy being silenced by epigenetic factors such as DNA methylation[2]. PWS occurs in one out of every 10,000 to 30,000 births, and affects males and females with equal frequency, of all races and ethnicities[3-5]. PWS is generally characterized by short stature, weak muscle tone (hypotonia), feeding difficulties, poor growth, delayed development, intellectual disabilities, small hands and feet, growth hormone deficiency (GHD), hypogonadism, uncontrolled appetite (hyperphagia), obesity, and diabetes mellitus. A pathological increase of appetite begins from 2 to 4 years of age, and leads to chronic overeating and obesity with persistent short stature[6]. Although the main cause of this is not yet clearly identified, it is known that hypothalamic dysfunction may affect abnormalities of the somatotropic axis and developmental delay[7]. The prevalence of GHD in PWS was 45%–80%, depending on the database and diagnostic criteria used[8,9]. According to clinical research that compared children with exogenous obesity to those with PWS[5,10], PWS resembles the phenotype of GHD more than exogenous obesity in growth velocity, skeletal maturation, growth hormone (GH) secretion, and the level of GH-dependent proteins. Even in infants and toddlers with otherwise normal BMI, when compared to normal children of the same age, increased fat mass and a decreased volume of smooth muscle were found[11].

GH treatment and methods which relieve the symptoms of associated disorders such as adrenal insufficiency, hypogonadism, hypothyroidism, diabetes mellitus, and appetite management are used in order to treat PWS[12]. Recombinant human growth hormone (rhGH, Genotropin®; Pfizer, Inc., New York, NY, US) was approved by the United States (US) Food and Drug Administration (FDA) for the indication of "growth retardation due to PWS" since 2000 and was approved in Europe including the "improvement of body composition"[5,12,13]. The benefits of GH therapy

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for children with PWS are well established, including positive action on linear growth, body composition, motor function, and psychomotor development[14-20]. The greater effects are observed in the first years of life, thus indicating the early institution of GH treatment for children with PWS between 4 and 6 months of age[5,14,21]. During childhood, long-term GH treatment with careful surveillance of the risks allows complete recovery from growth defects, normalizes their final adult height, and is associated with an increase of lean body mass (LBM), adiponectin levels, and head circumference[22-25]. After 8 years of GH treatment for patients with PWS, the standard deviation score (SDS) for height (Ht) and head circumference (HC) have completely normalized. Insulin-like growth factor-1 (IGF-1) SDS increases during the first year of treatment and remains stable[23]. In Korean pediatric patients with PWS, more than 2 years of GH therapy showed similar effects and resulted in increased Ht, HC, and IGF-1 SDS, LBM, and improved motor development[26,27]. Moreover, in adults with PWS, GH therapy also improved their body composition in terms of LBM and fractional body fat, and their thyroid hormone levels without glucose impairment[28].

GH therapy is effective in increasing muscle strength and motor skills, as well as improving mental speed, flexibility, health-related quality of life, and cognition and behavioral issues in the pediatric and adult population with PWS. In South Korea, a phase 3 clinical trial for Eutropin® (NCT02204163) in pediatric PWS was conducted by LG Chem, Ltd. to gain approval from the Ministry of Food and Drug Safety (MFDS). However, there is little literature on several topics related to the role of GH therapy in the life-long care of these patients. In this light, further research is required to improve our understanding of the physiopathology of GH/IGF-I axis during the entire lifespan of PWS subjects. More detailed knowledge of the therapeutic targets of GH administration is also needed, aiming to optimize the clinical management of these individuals. Simultaneously, the role of concomitant therapies such as sex steroids, dietary treatment, physical therapy, and inhibition of hyperphagia on the effects of GH administration should be clarified. Since most of the current studies are short-term and uncontrolled, long-term surveillance of the benefits and risks of GH therapy is strongly recommended for patients with PWS, in order to obtain definitive data on the safety of this treatment.

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