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Advances in Chinese and Western medicine for idiopathic dwarfism

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Abstract: In recent years, with the improvement of living standards, the nutritional status of children in China has improved significantly, but the situation of short stature in children is still not optimistic, short stature and malnutrition are still relatively common problems in the process of children's physical growth, especially in preschool children, therefore, the author summarizes the research progress of Chinese and Western medicine in the treatment of short stature in children, so as to guide the clinical treatment of short stature in children.

1. Introductions

Short stature is defined as an individual whose height is less than 2 standard deviations (-2 SD) from the mean height of a normal population of the same race, sex, region, and age in a similar environment, or less than the 3rd percentile of the normal child growth curve. Endocrine disorders often cause short stature in children, but some children with short stature are normal physiological variables [1]. The causes of short stature in children are complex, but it is now believed that the secretion and dysfunction of growth hormone-insulin-like growth factor, sex hormones, thyroid hormones, and other related growth factors can cause short stature in children, so it is very important to identify and diagnose early in clinical practice. In this paper, we review a large number of books and materials on the treatment of short stature in children from different perspectives of Chinese and Western medicine, and provide the following review, aiming to provide more ideas and methods for the treatment of short stature in children, which is of practical significance for future research on the treatment related to short stature in children.

2. Progress in the study of the pathogenesis of idiopathic dwarfism in Western medicine

Short stature is a common clinical manifestation, and as such it is widely believed to be a polygenic trait. However, recent studies [2] have recently challenged this view, suggesting that many children classified as idiopathic short stature may have single gene defects, and this report points to a number of single gene defects as the cause of the growth disturbances observed in non-syndromic children. Most of these defects are present in genes associated with the growth plate cartilage and growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis, and affected patients usually show the

mildest form of some form of skeletal dysplasia, or subtle abnormalities in laboratory tests indicating hormone resistance or anhedonia. Costantini et al [3] reviewed the latest in short stature skeletal disorders genetic findings, reporting that there are studies in the spine, which identified the aggregated proteoglycan gene (ACAN), an osteochondrogenic gene in which heterozygous mutations [4] cause autosomal dominant short stature and accelerated skeletal maturation. Foreign studies [5] have shown that heterozygous mutations in ACAN can lead to mild skeletal dysplasia, with clinical manifestations of short stature and early bone age. Recent genetic findings in epiphyseal dysplasia, vertebral epiphyseal dysplasia and some monogenic forms of isolated dwarfism. type C natriuretic peptide (CNP) and its major receptor natriuretic peptide receptor B (NPR-B) have been shown to be important in skeletal development [6], and it has been reported [7] that heterozygous NPR2 natriuretic peptide receptor2 mutations were found in 6% of patients initially classified as ISS, in which affected patients had Mild and variable degrees of short stature, suggesting that heterozygous mutations in NPR2 may be an important cause of familial short stature in nonsyndromic conditions. Hisado-Oliva et al. in an ongoing whole-exome sequencing study [8], resulted in the identification of two heterozygous NPPC mutations located in the highly conserved CNP loop, both showing a significant reduction in cyclic guanosine phosphate synthesis, confirming their the pathogenicity of NPPC mutations was demonstrated for the first time in humans with autosomal dominant short stature.

3. Western medicine drug treatment

3.1 Recombinant human growth hormone (rhGH)

Growth hormone deficiency is more common in children with pathological short stature, and some literature [9] reported that about 30% of children with short stature were diagnosed with growth hormone deficiency. Lu Chen et al. [10] suggested that recombinantly expressed rhGH is equivalent to human endogenous growth hormone in promoting growth and development, and that growth hormone stimulates local production of IGF-1 in chondrocytes and proliferates chondrocytes, promoting accelerated linear growth and skeletal widening. At the same time, growth hormone induces vitamin D activation, which synergizes with sex hormones and calcitonin, allowing for better calcium absorption into the bone. Therefore, short stature in children due to growth hormone deficiency can be achieved by growth hormone supplementation to promote growth and development. In a review of 50 cases of children with idiopathic dwarfism, Wang Shuhua [11] found that the effect of recombinant human growth hormone in children with idiopathic dwarfism was significant, and the difference was statistically significant ($P < 0.05$), which could effectively promote the growth of children and regulate the bone metabolic index. Growth hormone deficiency (GHD) is the first indication for which rhGH is approved by FDA in the U.S. The diagnosis of GHD is based on: 1) height that meets the criteria for short stature; 2) annual growth rate that is significantly lower than that of children of the same age; 3). At least two GH stimulation tests with a peak value of less than 7-10 μg/L; 7. In general, replacement therapy with rhGH in patients with GHD can significantly promote growth catch-up and help increase adult lifetime height. A foreign study [12] assessed the benefits by retrospectively analyzing the experience of 123 children with ISS treated with 0.32 ± 0.03 mg/kg/week rhGH and comparing it with 305 untreated historical controls from 9 different randomized and non-randomized controlled studies, showing that rhGH is important for normalization of height and growth in children during childhood and for achieving normal adult The results showed that rhGH was very positive for normalization of height and growth in children during childhood and for achieving normal adult height (the two main goals of treatment), that the treatment was safe, and that there were no significant adverse events. Liu Hongli [13] et al. applied rhGH treatment to children with ISS significantly improved their GV, significantly increased serum IGF-1 levels in children, and better promoted height growth.

However, there are foreign reports [14] that combined rhGH and GnRH analogue therapy in adolescents with normal pubertal dwarfism does not increase their final height above the predicted adult height before treatment; moreover, the cost and expense of these drugs are high and this form of treatment is not recommended clinically. Therefore, there is some controversy regarding the clinical use of recombinant human growth hormone.

3.2 Aromatase inhibitors (AI)

The main role of aromatase (aromatase) [15] is to catalyze the conversion of androstenedione and testosterone to estradiol and estrone, which are rate-limiting enzymes for estrogen biosynthesis. Estradiol has a very important role in both bone growth and mineralization. Compared with the first and second generation aromatase inhibitors, the third generation such as letrozole and anastrozole can effectively inhibit estrogen levels with high selectivity, reversibility and fewer adverse effects. At the same time, the treatment with AIs can create hyperandrogenemia, which directly acts on the growth plate and has a pro-linear growth effect, thus improving the adult height of pubertal dwarf children without inhibiting the development of male secondary sexual characteristics and without causing negative psychological effects on the children. Foreign studies have shown [16] that estrogen is an important regulator of bone maturation, growth plate fusion, and longitudinal growth arrest in both males and females. Reduced bone maturation and increased PAH can be achieved in boys with idiopathic short stature (ISS) by blocking estrogen biosynthesis using aromatase inhibitors.

However, some clinical studies [17] found that aromatase inhibitors are at risk of adverse drug reactions such as liver and kidney function damage, lipid metabolism disorders and bone metabolism disorders, and the long-term effects on male reproductive system damage and bone metabolism are not clear. Therefore, aromatase inhibitors need to be weighed against the pros and cons in clinical practice and treatment options should be carefully selected.

3.3 Insulin-like growth factor (IGF-1)

IGF-1 [18] is a key mediator in the growth-promoting effects of growth hormone, and serum IGF-1 concentration is positively correlated with growth hormone dose and height improvement. In some countries, IGF-1 has been approved for the treatment of short children with severe IGF deficiency and normal growth hormone secretion (insensitivity to growth hormone) [19]. During clinical practice, its effectiveness [20] is still under observation.

It has been reported abroad [21] that although dual treatment with GI and IGF-I may contribute to metabolic outcomes, a published study of a combined approach to treating children with non-GH deficient short stature showed insignificant height gains compared to GH alone.

3.4 Gonadotropin-releasing hormone analogs (GnRHa)

GnRHa binds to GnRH receptors in anterior pituitary gonadotropic cells, initially promoting a transient increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) release, followed by a downregulation of the corresponding receptors in pituitary target cells, inhibiting the pituitary-gonadal axis and decreasing the secretion of LH, FSH and gonadotropins, thereby controlling the sexual development process and delaying skeletal maturation. GnRHa significantly inhibits the rapid progression of bone age and early epiphyseal closure in children with ISS, thereby improving PAH and FAH. The combination of gonadotropin-releasing hormone analogs and anabolic steroid hormones has been found to increase height at puberty [22] [23] with satisfactory clinical outcomes.

However, it has been reported [24] that GnRHa continues to reduce BMD, with 69% of children in

the treated group having a lower BMD than the mean value of -1SD in the normal population [16]. Given the unsatisfactory efficacy and adverse effects of GnRHa alone, it is not recommended for use alone in children with ISS and should be used with clinical caution.

4. Chinese medicine treatment

4.1 Internal treatment method

In recent years, Chinese medicine has been paying more and more attention to the research of short stature in children, and after reviewing the relevant literature, most traditional medicine studies and treats short stature in children from the "holistic concept" and "diagnosis and treatment". Chinese medicine believes that the cause of short stature in children is closely related to the spleen, liver and kidney, the kidney is the origin of the congenital, the main collection of essence, the main growth and development, the spleen is the origin of the postnatal, the source of Qi and blood biochemistry, the congenital essence of children's growth and development depends on the postnatal water and grain essence moistening, the liver is the main drainage, the main blood collection, in the body together with the tendons, its Hua in the claws, has the physiological characteristics of the main rise and development, through the spring qi, expressed as rising and growth and vitality. The etiology of short stature in children is mostly related to deficiency of kidney essence, weakness of spleen movement, deficiency of liver and blood, and lack of nourishment of tendons and bones. Spleen and kidney deficiency is the root of the disease, and liver and blood deficiency is the symptom of the disease [25]. According to Zhang Yu [26], the diagnosis and treatment of short stature in children can be based on "spleen" as the core, and spleen and earth transportation is the basis for filling the four sides and honoring the four limbs, on this basis, the treatment of children with different stature is based on the identification of evidence. Wang Yajun et al. [27] proposed the prevention and treatment of short stature in children from the liver based on the physiological characteristics of the liver, and the treatment of short stature in children in Chinese medicine should seize the golden season of growth in spring, and use drugs to regulate the liver and nourish the liver and pay attention to the regulation of emotions. According to Chen Rongkun [28], the disease of dwarfism originates from the spleen and kidney, and is blamed on the liver and wood, and is obstructed by blood stasis. Before development, we use Liu Jun Zi Tang as the basis for identifying and adding and subtracting, and after development, we treat males by activating blood stasis, warming the kidneys to help Yang, and benefiting essence to nourish the kidneys, and after development, we treat females by draining the liver and relieving depression, and nourishing blood to benefit essence.

Through a large number of clinical observations, it has been found that lung spleen qi deficiency is more common in children with short stature clinically [29]. "The lung is the pivot of vitality, and the spleen is the source of vitality", only when the lung and spleen organs work in coordination can they ensure the generation of zong qi and lifelong qi; the lung is a delicate organ, which is the main organ of qi and unites the skin and hair, and since children have delicate internal organs and are not yet full of formal qi, external evils are prone to invade the lung guard and cause disease; the spleen is the basis of the latter, which is the main organ of transportation and transformation and unites the muscles and limbs, but the spleen and stomach of children are not yet The two organs of the lung and spleen interact with each other and eventually become the symptoms of deficiency of both lung and spleen, which affects the development of the child, so the treatment should be to nourish the lung and benefit the qi, strengthen the spleen and help transport, improve the state of deficiency of the lung and spleen of the child, so as to accelerate the growth of the child [30]. In the above reports, the treatment was based on the identification of different internal organs and achieved good clinical results.

4.2 External treatment method

According to Chinese medicine, the absorption of nutrients is related to the spleen and stomach. If a child's diet is disordered, or if the spleen and stomach are weak due to illness, the spleen and stomach will not be full of qi and blood, and the organs will not be nourished, which may cause the child's growth and development to be slow. Wu Shiji, an expert in external treatment in the Qing dynasty, wrote in his "Li Bo Era" that "the theory of external treatment is the theory of internal treatment, and the medicine of external treatment is the medicine of internal treatment, but the only difference is the method" [31]. In recent years, there have been more studies on the intervention of children's growth and development through acupuncture point patching, and all of them have achieved good clinical efficacy. For example, Yayun Ye [32]'s self-designed pediatric growth patch consists of one She medicine and eight Chinese herbs (Jingbanbiancao, Cinnamon, Chaihu, Poria, Atractylodes macrocephala, Bai Shao, Angelica sinensis, Cumin, Fried Chicken Neijin, and Salt), which can treat the liver and spleen together, suppress wood and help earth, regulate the liver and spleen, and treat idiopathic short stature in children with earth deficiency and wood hyperactivity. The efficacy is remarkable, and the side effects for the children are small, so the clinical application prospect is good.

Zhang Hongyan [33] believes that improving the function of the spleen and stomach, promoting nutrient absorption is the fundamental treatment of this disease, through pediatric massage (using massage techniques such as chiropractic, abdominal massage, pinching the four transverse lines, can be combined with acupuncture, traditional Chinese medicine conditioning), point pressure on the Hall of Yin point, press and knead the Baihui point, pound the small Tianxin point, divided into yin and yang, while pressing and kneading the Banmen point, Shenmen point, to achieve "Banmen plus Shenmen, eliminate food and calm the mind ". Based on the theory of "regulating the transportation hub", Xiang Hong [34] et al. regulated the transportation hub of the spleen and stomach to promote the smooth functioning of the spleen and stomach of the child, so that blood and qi could reach the middle jiao and the spleen and stomach could be restored to health. In the clinical process, the clinical efficacy of "regulating the transportation hub" massage technique based on meridian and acupoint theory combined with recombinant human growth hormone in the treatment of children with idiopathic dwarfism was good, and it could significantly improve the growth rate of the children, and no significant adverse effects were observed, and the safety was good, so it is worthy of clinical application.

Acupuncture at the Four Sutures point can increase the serum insulin-like growth factor and prealbumin levels in children, promoting growth and tonifying Qi and blood. For some children with dwarfism who are deficient in growth hormone and have small bone age, acupuncture at the Sijian point together with the method of eliminating accumulation and regulating spleen (patchouli, atractylodes, chenpi, thick park, hen's inner gold, prunus, jiao hawthorn, fried grain buds, poria, yam, and hu huanglian) can improve the deficiency of insulin-like growth factor and promote the growth rate without accelerating the healing of bone age.

5. Psychotherapy

According to Liu Shiping [35], in the treatment of dwarfism, the long treatment period and expensive treatment, as well as the need for children to undergo regular invasive examinations during the treatment process, make children lack self-confidence and anxiety, which inhibit the secretion of growth hormone and other hormones, and to a certain extent will affect the recovery of the disease. Therefore, while treating dwarfism with recombinant human growth hormone, close attention should be paid to the psychological condition of the children and targeted interventions should be given, so as to improve the treatment effect and the quality of life of the children and reduce the psychological

burden of the children. Li Huahua [36] found that children with idiopathic short stature have different degrees of psychological anxiety and depression, and the combination of recombinant human growth hormone and psycho-behavioral interventions for children with idiopathic short stature can significantly improve the growth rate of children, and also has some clinical value for improving the adverse psychological conditions.

6. Conclusion

With the accelerated pace of industrialization and the change of ecological environment, research related to short stature in children has attracted attention. By reviewing medical books and materials, we can find that Western medicine often uses growth hormone and hormone therapy to treat short stature in children, and has achieved some results, while there are also reports of adverse effects of such diagnosis and treatment. In contrast, Chinese medicine has also achieved more satisfactory results by using a combination of evidence-based therapy and Chinese health theory. The treatment of short stature in children by TCM is mostly based on evidence-based typology in the early stage, but recently, external treatments such as acupuncture point application, acupuncture, moxibustion and massage are common, which still need to be explored in depth in order to improve their efficacy. Perhaps the flexible and discriminative use of internal and external treatment of TCM and Western medicine, the combination of each method, mutual achievement, more likely to achieve a satisfactory final height, more improve the long-term efficacy, clinical application of good prospects.

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