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Genetic causes of short stature in children

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Abstract

One of the essential elements of a visit to a pediatrician is a height measurement, which allows for the presentation of the child's growth tendency. Short stature is defined as a height that is lower than the average of a specific population, adjusted for age and sex, by at least 2 standard deviations, i.e., less than the 3rd percentile. Due to accompanying symptoms or their absence, the suspected etiology may vary. Genetic disorders are significant causes of short stature, especially among pediatric patients. The division distinguishes chromosomal, monogenic and polygenic disorders. Other possible causes of short stature may be the coexistence of chronic diseases or disorders of the endocrine system. In the case when the growth disorder is not a pathological condition, a variant of normal growth is diagnosed. In the diagnosis of short stature, in addition to a physical examination, it is sometimes necessary to perform laboratory or radiological tests, genetic tests, and specialist consultations.

Material and methods: A review of the available literature of the PubMed database from 1976 to 2024.

Keywords: short stature, genetics, genetic syndrome, genetic disorder

Introduction

One of the essential elements of a visit to a pediatrician is a height measurement, which allows for a clear and transparent presentation of the child's growth trend. Through measurements conducted during check-ups by a doctor, as well as at home by a parent, it is possible to estimate the child's physical development and notice even slight disorders, expressed as standard deviations (SD) from the normal population mean for children of a given age and sex. [1]

Short stature is defined as a height that is lower than the mean of a specific population, adjusted for age and sex, by at least 2 standard deviations (SD), i.e., less than the 3rd percentile (pc). It is estimated that short stature affects about 2.3% of the population. [2, 3]

The term tall stature is defined as a height that is at least 2 SD above the mean of a specific population, adjusted for age and sex, i.e., greater than the 97th percentile. [4] The incidence of tall stature is comparable to the incidence of short stature, while this disorder is a less common problem in subspecialist care. [3]

According to studies conducted in the last century, genetic inheritance plays a large role in human height. It has been shown that the height of adopted children correlates primarily with the height of their biological parents, and to a lesser extent with the height of the adopted parents. [5]

In turn, a study analyzing the height of 6,752 people from 2,508 families estimated that the heritability of height ranges from 75% to 98%. [6]

Epigenetic inheritance should also be considered as a factor determining adult height and that may explain changes in height over generations. [7]

For this reason, in the diagnosis of short stature, it is necessary to take into account not only the patient's history, but also his family history and the influence of social conditions. Sometimes, in addition to a physical examination, it may be necessary to perform laboratory or radiological tests, genetic tests, and specialist consultations. [1]

Causes of short stature in children

In an analysis of 86 children with short stature, 6 causes were mentioned, the most common of which was idiopathic short stature (ISS, 41%), followed by growth hormone deficiency (GHD, 29%) and genetic diseases (14%). [8]

Considering the classification of short stature, it should be remembered that not every disorder is a pathological condition.

Variants of normal growth

Among the variants of normal growth, the most prominent are familial short stature, constitutional delay of growth and puberty (CDGP) and small for gestational age (SGA) with catch-up growth (Table 1). [1] In almost half of the cases, the cause of short stature cannot be determined and then **idiopathic short stature** (ISS) is diagnosed. This is a diagnosis of exclusion. [1, 8, 9] Depending on whether the disorder runs in families or not, the patient is diagnosed with familial (genetic) short stature or non-familial short stature. [1, 9] Children with ISS usually reach a height below 2.3 pc, while their parents' height is usually below 10 pc. No other abnormalities are observed, and the results of the tests performed remain normal. Treatment is not required. Genetic consultation and monitoring of the child's growth are recommended. [1]

Constitutional delay of growth and puberty (CDGP) is one of the most common causes of both delayed puberty and short stature. It affects more than 2% of adolescents, mostly boys. [10] The birth length of children with CDGP is normal, and growth retardation occurs during the first 3 years of life. Regular growth is then observed, but the growth spurt during puberty occurs later than average. There is no targeted treatment. Growth monitoring and genetic counseling are primarily recommended. Alternatively, in some cases, a short testosterone therapy in boys or estrogen therapy in girls is used. [1, 10]

Small for gestational age (SGA) refers to infants born with a birth weight and/or length at least 2 SD below the mean for gestational age and sex, which corresponds to 2.3 pc. Most patients (85-90%) with SGA with catch-up growth achieve normal height by 2 years of age. In patients who fail to achieve expected height, growth hormone therapy is recommended. [1]

SGA should not be confused with intrauterine growth restriction (IUGR), which refers to infants with a confirmed cause of prenatal growth restriction. [1]

<table>
<tr><th colspan="2">Short stature</th></tr>
<tr><th>Variants of normal growth</th><th>Pathological growth patterns</th></tr>
<tr><td rowspan="3">1) Idiopathic short stature (ISS)
a) Familial (genetic) short stature
b) Nonfamilial short stature
2) Constitutional delay of growth and puberty (CDGP)
3) Small for gestational age (SGA) with catch-up growth
4) Early puberty with accelerated growth, maturation and early epiphyseal fusion</td><td>1) Chromosomal defects, e.g.:
- Down syndrome
- Turner syndrome
- DiGeorge syndrome
2) Single gene defects
a) Defects that directly compromise components of the GH/IGF axis
b) Defects responsible for causing syndromic short stature by compromising intracellular signaling pathways or fundamental cellular processes
c) Defects that cause skeletal dysplasia
3) Polygenic conditions</td></tr>
<tr><td>Chronic systemic diseases, e.g.:
1) Chronic kidney disease
2) Crohn’s disease
3) Juvenile idiopathic arthritis
4) Nutritional deficits
5) Gluten enteropathy
6) Cystic fibrosis
7) Hematologic or solid malignancies</td></tr>
<tr><td>Endocrine system dysfunction with abnormal production of growth hormone or other hormones, e.g.:
1) Growth hormone deficiency
2) Hypopituitarism
3) Hypothyroidism
4) Cushing syndrome</td></tr>
</table>

Table 1. Division of causes of short stature [1, 2, 9]

Pathological causes of short stature

The division, dividing the pathological causes of short stature, distinguishes three main groups of diseases (Table 1). [1] Genetic disorders are significant causes of short stature,

especially among pediatric patients. The division distinguishes chromosomal, monogenic and polygenic disorders.

Chromosomal disorders include numerical aberrations, such as Down syndrome and Turner syndrome, and structural aberrations, such as DiGeorge syndrome and Prader-Willi syndrome. [2]

Down syndrome, caused by trisomy 21, occurs in 1 in about 700 children born in the United States. [11] It is associated with disabilities, both physical and mental. One of the most common disorders in patients suffering from this condition is a congenital heart defect, occurring in about 60% of infants with Down syndrome. Sometimes, pulmonary hypertension develops, the frequency of which can be reduced by early diagnosis and treatment of obstructive sleep apnea, aspiration, or recurrent lower respiratory tract infections. Autism spectrum disorders, attention deficit disorder, and epilepsy are also observed, as well as congenital anomalies of the digestive system and kidneys. Autoimmune diseases, diabetes, celiac disease, and thyroid disorders also develop more often than in the general population. [12] One study conducted at The Children's Hospital of Philadelphia involved 637 participants from 25 states. 1520 measurements were obtained, which were collected in the years 2010 to 2013. Measurements were omitted if the patient's condition was advanced, i.e. if they suffered from other, additional genetic disorders or were undergoing anticancer therapy. It was found that children with Down syndrome had lower height and smaller head circumference, compared to the reference charts. However, the body weight of these children differed to a lesser extent from the average population. [11]

Turner syndrome, which is caused by monosomy X of the chromosome, affects 50 in 100,000 women. [13] It is a disorder that primarily affects growth disorders. [13, 14] Patients who have not received growth hormone therapy are 20 cm shorter than the general population adjusted for sex and age. [14] The growth pattern is also different from the average. [13, 14] Growth retardation begins already in prenatal life and is observed mainly in the first years of life, which is why growth hormone treatment can be proposed from the age of 2, if the appropriate criteria are met. Increasingly, attention is also paid to other disorders in these patients, such as problems with puberty and fertility, cardiovascular abnormalities, and the impact on mental health. [13]

DiGeorge syndrome, also known as 22q11.2 deletion syndrome, occurs in approximately 1 in 4,000 births. [15, 16] The disorders observed in these patients include primarily immunodeficiencies, cardiac, renal and ocular anomalies, hypoparathyroidism, as well as skeletal defects and developmental delays. [15] The study conducted by Alex Habel et al. included 818 patients aged from birth to 37 years. Height, weight and head circumference were

measured. Patients with additional genetic disorders, hemiplegia and scoliosis were not included in the study. A decrease in the mean height for both sexes was noted from 50 pc at birth to 9 pc at 9 months of age, and this condition persisted until 5 years of age. The growth curves were leveled at 17 years for boys and 16 years for girls. [16]

Prader-Willi syndrome is a relatively rare disorder, with an estimated incidence of 1 in 10,000-30,000. It develops as a result of the lack of expression of paternal genes from chromosome 15q11.2-q13. In the absence of growth hormone supplementation, short stature almost always occurs in the second decade of life. There is no growth spurt during puberty. The average height of an untreated male is 155 cm, and that of a female is 148 cm. Reduced secretion of growth hormone is considered as a possible etiology. Other symptoms of Prader-Willi syndrome include primarily hypotonia, which impairs sucking, resulting in feeding disorders in early childhood. Then, in later infancy or early childhood, morbid obesity develops, associated with excessive eating. Cognitive disability, tantrums, and hypogonadism with genital hypoplasia and often infertility also occur. [17]

Monogenic disorders include three main groups of abnormalities, for which the affected genes are responsible: defects that directly compromise components of the GH/IGF axis; defects responsible for causing syndromic short stature by compromising intracellular signaling pathways or fundamental cellular processes; defects that cause skeletal dysplasia. Examples of monogenic disorders are achondroplasia and Leri-Weill dyschondrosteosis. [2]

Achondroplasia is the most common form of dwarfism. It is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 (FGFR3). 80% of cases are sporadic. It occurs in 1 in 15–25,000. Characteristic features include disproportionate shortening of the proximal skeletal segments, macrocephaly, hearing loss, and a reduced size of the foramen magnum. Because of the lack of documented effect of growth hormone in the treatment of short stature in achondroplasia, this therapeutic method is not routinely recommended. New therapies targeting FGFR3 signaling are currently being developed. [18]

Leri-Weill dyschondrosteosis is diagnosed in the presence of a pathogenic SHOX variant or a deletion, duplication, or insertion involving the SHOX coding region and/or an enhancer region regulating SHOX expression. The classic clinical triad includes short stature; mesomelia, where the mid-limb is shortened relative to the proximal part; and Madelung deformity, which is malalignment of the radius, ulna, and carpus at the wrist. Growth hormone administration can increase final height by 7–10 cm. [19]

In **polygenic disorders**, short stature results from the overlap of several common variants, in contrast to monogenic disorders, in which a rare variant has a large impact on the phenotype—both short stature and other features of the genetic syndrome. A GWAS study conducted by The Genetic Investigation of ANthropometric Traits (GIANT) consortium identified 697 variants that had a significant impact on height. [2, 20]

Chronic diseases that may be accompanied by short stature are presented in Table 1. One of the most common diseases that may lead to impaired growth is chronic kidney disease. This is associated not only with nutritional, hormonal and metabolic disorders, but also with long-term corticosteroid therapy. About 50% of children and adolescents with Crohn's disease suffer from short stature, and about 90% are underweight. In turn, long-term inflammation, stiffening and deformation of the affected joints in 10-40% of children with juvenile idiopathic arthritis leads to short stature. In many cases, delayed puberty is also observed. The main therapeutic points are primarily monitoring the patient's condition and, if necessary, referring him to a specialist. Sometimes, performing special laboratory tests or diagnostic procedures may be necessary. Patients should be provided with adequate nutrition and optimized treatment of the underlying disease. [1]

Short stature may also be the result of endocrine system dysfunction with abnormal production of growth hormone or other hormones in conditions such as growth hormone deficiency (mentioned above as a genetic cause of short stature), hypopituitarism, hypothyroidism and Cushing's syndrome. [1]

Conclusions

There are many causes of short stature in children. Both physical examination, laboratory tests, and specialist additional tests allow us to draw suspicions regarding the possible etiology. A holistic approach to the patient and consideration of all possible options are necessary. Although progress in the development of medicine is very noticeable, many questions still remain unresolved. Further research into the possible causes of short stature and improvement of diagnostic methods are necessary to fully help each patient.

Disclosure statement

Author's contribution

All authors contributed to the article.

Conceptualization, J.I., and J.I.; methodology, M.S.; software, M.B.; check, D.F., M.M. and D.Z.; formal analysis, J.S.; investigation, D.S.; resources, J.I., J.I., M.S., M.B., D.F., M.M., D.Z., J.S., D.S., M.K.; data curation, M.K.; writing - rough preparation, J.I., J.I., M.S., M.B., D.F.; writing - review and editing, M.M., D.Z., J.S., D.S., M.K.; visualization, J.I., J.I., M.S., M.B., D.F.; supervision, M.M., D.Z., J.S., D.S., M.K.; project administration, J.I., J.I., M.S., M.S.

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