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Review/Praca poglądowa

Idiopathic short stature, current knowledge and perspectives – Review article

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INFORMACJE O ARTYKULE

Historia artykułu:
Otrzymano: 23.10.2016
Zaakceptowano: 03.01.2017
Dostępne online: xxx

Keywords:
- Idiopathic short stature
- Etiology
- Treatment
- Growth hormone

ABSTRACT

Short stature (SS) is a frequent cause of referral to endocrine clinics and is also a widely researched condition in the literature. Idiopathic short stature (ISS) is diagnosed when a list of known causes of SS had been ruled out. The aim of this article is to draw attention of pediatricians to what is new in the ISS diagnosis and to introduce to the ISS problem some new entries which can be further researched if needed.

It was a challenge to define and categorize ISS anew in the light of some substantial progress gained in this field in the last decade. The aforementioned progress pertains usually to one of the three following categories: (1) exposing underdiagnosed genetic syndromes with minimal dysmorphic features, for instance Noonan syndrome, SHOX deficiency or rasopathies and finding new mutations in known genes, (2) proving new strategies to identify genetic causes of short stature effective, especially the perspectives opened by whole exome sequencing (WES) which can well identify monogenic disorders known to cause growth disorders and; (3) approaches focused on metabolic or paracrine mechanisms, among them studies of ghrelin influence on height and vitamin D receptor gene polymorphisms in ISS patients, not forgetting simple but vital means as working in a multidisciplinary team.

Clinicians caring for SS children are frequently in difficult diagnostic situation. Therefore reliable sources of reference and sharing of clinical experience are of great value in the diagnostic process of ISS.

Introduction

Growth is determined mainly by genetic factors. Analyses of adult height and studies of twins indicate that the heritability for adult height ranges between 75 and 90% [1]. About 20% of adult height is due to environmental factors. Growth is a polygenic trait and the measure of contribution of various genes responsible for growth to reach adult height is unknown.

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http://dx.doi.org/10.1016/j.pepo.2017.01.001

Artykuł w formie *in press* proszę cytować jako: Rohde A, Obara-Moszynska M. Idiopathic short stature, current knowledge and perspectives – Review article. Pediatr Pol. (2017), http://dx.doi.org/10.1016/j.pepo.2017.01.001

There are many known genes associated with the determination of growth: genes responsible for GH secretion and action, for example *GH1, HESX1, LHX3, GHR, IGF-1R* and genes associated with skeletal growth response such as *BMPs, CNP, FGF, FGFR3, IHH*. Since epiphyseal plate is where growth takes place, pathophysiological classification of SS caused by genetic factors seems most adequate [2].

Short stature is a relative term and refers to children whose height is more than 2 SD below the corresponding mean height for given age, sex and population. About 3% of the population is below the normal range of height, so meets the criteria of short stature. These children are mostly healthy, diagnosed with constitutional delay of growth and puberty or familial short stature, and some of them are diagnosed as having idiopathic short stature. The term 'idiopathic' is of Greek origin and means one's own disease or suffering. The principle of causality makes one wonder though if the causes only need to be uncovered. It is widely agreed that ISS is a diagnosis by exclusion. Any evidence of chromosomal, endocrine, systemic or nutritional abnormalities rules out ISS. The definition of force in the past authored by KIGS specifies also that 'children with ISS have normal birth weight and are GH sufficient' [3].

Consensus Statement on the Diagnosis and Treatment of Children with ISS (Consensus) issued in 2008 stresses the need of stimulated GH levels for the diagnosis but sees MRI as not necessary in the process [4]. According to the Consensus approximately 60–80% of all short children at or below −2SD fit the definition of ISS.

In 2016 ICPED expanded the definition as follows: 'no psychiatric disorder, no severe emotional disturbance, no evidence of endocrine deficiency. The tempo of growth may either be slow or normal.' The ICPED classification of ISS is clear. Depending on whether child's height is within the 'normal' range for parental height or not, ISS is either familial or non-familial. Further subcategories are based on the timing of the onset of puberty [5]. The trend of genetic research paves the way to ISS being diagnosed less often but at the cost of a more time-consuming and meticulous procedure because the list of exclusions lengthens and more specialist consultations and genetic tests are required. Known etiology of SS is divided in disproportionate and proportionate of prenatal or postnatal origin. This classification along with an intuitive algorithm for the diagnosis of SS can be found in an article by Argente published in 2015 [6]. This author concludes that congenial skeletal dysplasia must never be overlooked because it accounts for at least 436 disorders associated with SS.

The progress in uncovering causes of SS can be divided in 3 categories: (1) exposing/unmasking underdiagnosed genetic syndromes with minimal dysmorphic features and finding new mutations in known genes, (2) proving some new strategies to identify genetic causes of short stature effective and (3) alternative approaches focused on metabolic/paracrine mechanisms.

The aim of this article is to draw attention of pediatricians to what is new in the ISS diagnosis without extensive listing of all updates in the ISS classification and treatment, but rather to introduce to the ISS problem some new entries which can be further researched if needed.

Underdiagnosed syndromes and new mutations in known genes

Sometimes beneath an 'ISS label' physicians can discover rare genetic conditions with mild phenotype features such as Noonan syndrome [7], SHOX deficiency with minor abnormalities and also 3-M syndrome. Noonan syndrome (NS1), with estimated incidence of 1 in 1000 to 2500 live births, is caused in about 50% of cases by mutation of the *PTPN11* gene. Patients present facial dysmorphia: broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears; chest and spine deformities; congenital heart defects, among which pulmonic stenosis and hypertrophic cardiomyopathy are most frequent and delayed puberty [8]. In 3-M syndrome a severe pre- and postnatal growth retardation as well as radiological features (*e.g.* thin long bones, tall lumbar vertebrae, molar hypoplasia) are observed. 3-M syndrome is caused by mutations in *CUL7, OBSL1* or *CCDC8* genes [9]. If short stature is due to novel mutations in known genes, like for example in the Insulin-Like Growth Factor 1 Gene, the diagnosis takes usually longer [10].

SHOX mutations specific features are low extremities-trunk ratio [11], Madelung deformity and co-occurrence of disproportionate SS, short forearm and muscular hypertrophy [12]. Heterozygote SHOX mutations, mostly deletions, were detected in 2–15% of individuals classified earlier as ISS patients [13]. The use of phenotype scoring form comprehending the above mentioned features is an effective tool of referring patients to scanning of deletions and duplication of the SHOX gene [14]. Similar conclusions were drawn before by a multidisciplinary team including pediatric endocrinologists, pediatricians, radiologists, geneticists and epidemiologists gathered in Padua in 2011. It prepared recommendations to diagnose SHOX haploinsufficiency in patients classified prematurely as ISS. Among them are careful search for such signs as: distorted body proportions, above average BMI, Madelung deformity, *cubitus valgus*, short or bowed forearm and muscular hypertrophy [15]. If any such evidence is found, genetic testing should be done. Most laboratories use now MLPA for detecting copy-number variations (CNVs) of SHOX and its enhancers, followed by Sanger mutations screening.

On the other hand, it must be pointed out that in every short child body proportions should be measured and compared with age references, and that the term ISS should not be used for children with abnormal body proportions [16].

Nonsyndromic familial short stature (FSS) also included in the ISS definition can result from heterozygous mutations in the natriuretic peptide receptor B (NPR2) – this proved true for 6% of patients with ISS in a study conducted in 2013. It was known earlier that homozygotes present acromesomelic dysplasia type Maroteaux. Also, a failure to produce cyclic GMP after the stimulation of C-type natriuretic peptide in cells transfected with mutated NPR2 was established using *in vitro* cells-based assays. This mechanism is held responsible for growth impairment [17]. Patients with acromesomelic dysplasia type Maroteaux present disproportionate stature

Artykuł w formie *in press* proszę cytować jako: Rohde A, Obara-Moszynska M. Idiopathic short stature, current knowledge and perspectives – Review article. Pediatr Pol. (2017), http://dx.doi.org/10.1016/j.pepo.2017.01.001