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CASE REPORT

SETD5 gene mutation as the cause of short stature

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ABSTRACT

An 8-year-old boy was referred to the Clinic of Pediatric Endocrinology due to his short stature. The child comes from P II B II, was born naturally, with birth weight 2970 g. He had dysmorphism and a height of 118 cm (3rd centile). Growth hormone (GH) deficiency and other causes of short stature were excluded. A genetic panel was performed using next generation sequencing, which revealed a pathogenic variant in the *SETD5* gene, with which growth deficiency is not typically associated. Literature reports suggest that genetically determined conditions with transcriptional effects, GH deficiency, and intellectual disability may overlap phenotypically. The most likely cause of short stature in this case is a genetic mutation in the *SETD5* gene. The boy requires multidisciplinary care, including auxological assessment, growth monitoring, puberty assessment, and pediatric and endocrinological care. All children with short stature and dysmorphic features or body proportion abnormalities who receive GH therapy require genetic testing.

KEY WORDS:

***SETD5*, short stature, specific dysmorphia features.**

INTRODUCTION

Short stature is defined as body height being > 2 SD below the mean value or < 3rd centile for the age and gender of the child, or else as short for mid-parental height (MPH) is defined as a height centile more than 3 centile spaces below the MPH centile [1]. Growth is a highly sensitive indicator of the general state of the child; each chronic disease may reduce the rate of growth and finally be the cause of short stature [2]. A special algorithm is employed to determine the etiology of short stature in children (Figure 1).

Each child with short stature in whom dysmorphic features or body proportion disturbances are manifested should be diagnosed for certain genetic syndromes.

SET domain-containing 5 is a protein encoded by the *SETD5* gene (OMIM 615743); the protein belongs to the family of histone lysine methyltransferases. Mutations within this gene are closely associated with a rare developmental disorder known as autosomal dominant intellectual disorder 23 (intellectual developmental disorder, autosomal dominant 23; mental retardation syndrome 23 [MRD23] – OMIM 615761) with the gene locus *3p25.3*. The disorder is characterized by much lower than average general intellectual functioning associated with disorders of adaptive behavior, which is already manifested in the early developmental period. The mental retardation syndrome 23 patients additionally demonstrate such variable properties of the morphological phenotype as brachycephaly, low hair line, sunken bridge of the nose, elevated palpebral fissures (the palpebral fissures are situated superiorly and obliquely), narrow upper lip, and malocclusion defects manifested as crowding of teeth [3, 4].

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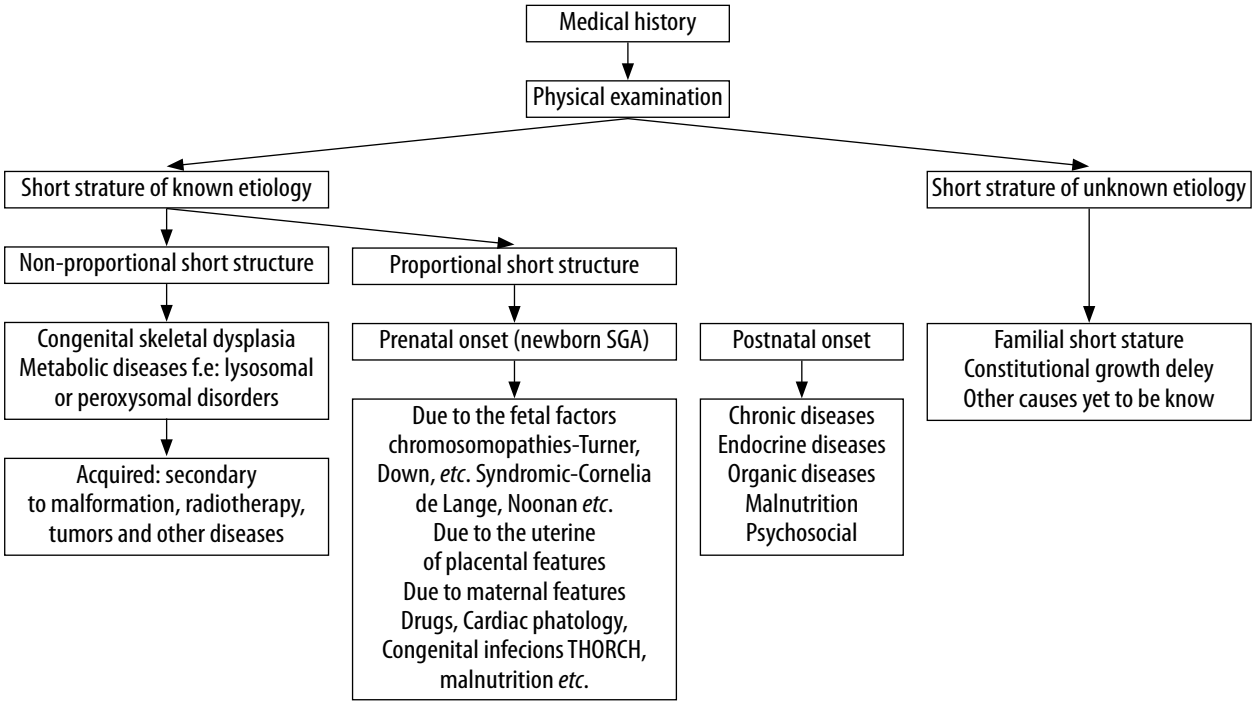

FIGURE 1. Diagnostic algorithm of short stature
SGA – small for gestational age

The objective of the report is to evaluate the association between the *SETD5* gene mutation and short stature.

MATERIAL AND METHODS

A retrospective clinical analysis of an 8-year-old boy diagnosed with short stature, dysmorphism and developmental delay was performed. The results of the 4-year diagnostics were evaluated. The boy is still under endocrinological care. Written consent of the boy's mother was obtained for the publication of test results and photos for scientific purposes.

CASE REPORT

A boy aged 8 years and one month was referred to the Department of Endocrinology due to his short stature. His birth history was as follows: second pregnancy, second delivery (April 20, 2010), born at 40 weeks of gestation after a spontaneous delivery. At birth, his general state was good (he received 8 points on the Apgar scale); his developmental parameters at birth were as follows: body weight 2970 g, body length (including body curvatures) – 53 cm, head circumference – 32 cm. His achievement of developmental milestones was delayed: the child demonstrated sitting and teething at 10 months and walked at 18 months of life. His speech development was also delayed; at the time of the visit to the department the boy continued to manifest problems with speaking and education and required a special educational profile.

Physical examinations performed during the hospitalization showed the boy's general condition to be good; the child did not show any signs of an infection,

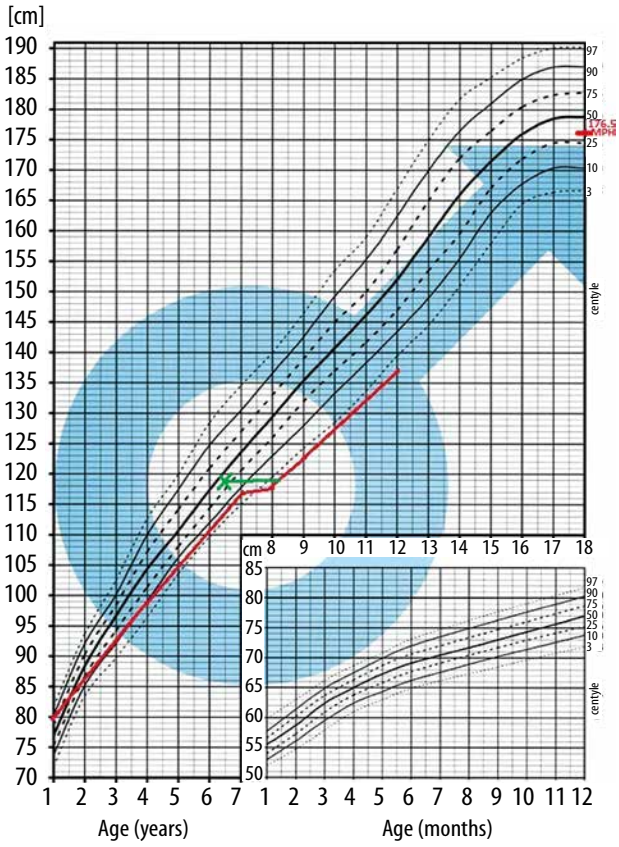

FIGURE 2. Patient's centile chart

his height was 118 cm < 3rd centile, body mass 24.3 kg (10th centile); his sex organs were prepubertal (Figure 2).

The following abnormalities were seen: microcephaly with brachycephaly, low-set deformed (asymmetric) earlobes, a relatively long philtrum, malocclusion including crowding of teeth. The prognosis of his final height based on the MPH was 176.5 cm. Hormonal tests demonstrated high growth hormone (GH) bursts (in the 24-hour test at

FIGURE 3. Photographs of patient

FIGURE 4. Photographs of patient

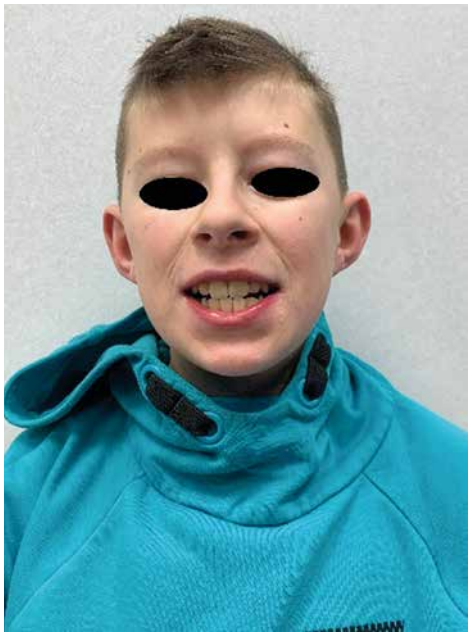

FIGURE 5. Photographs of patient

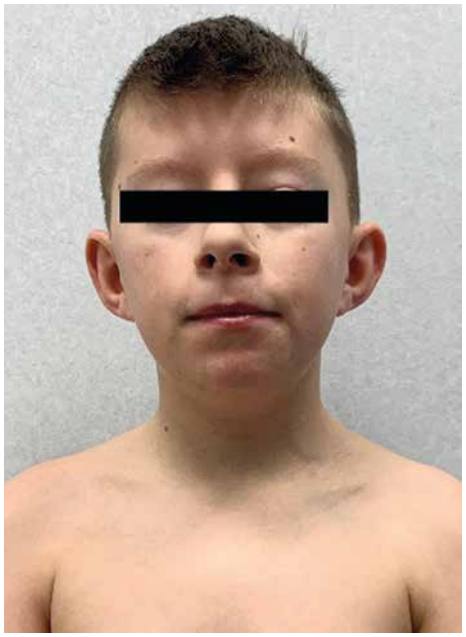

FIGURE 6. Photographs of patient

midnight > 40.0 ng/ml), his IGF1 concentration value was within the low normal level (63.5 ng/ml, N: 46–208 ng/ml), his Ft4 level was 0.950 ng/dl (N: 0.860–1.400), while his thyroid stimulating hormone was normal (2.360 µIU/ml, N: 0.6–4.84 µIU/ml). His bone age calculated in keeping with the atlas authored by Greulich corresponded to his chronological age, i.e. 6–7 years of life. Due to his intellectual disability (ID) and specific morphological phenotype, the KBG* syndrome was suspected. The gene test panel was performed using next generation sequencing (NGS) analysis. The tests demonstrated the presence of the pathogenic variant of the *SETD5* c.1945G>Tp. (*Glu 551Ter*) gene, as well as the c.452G>A p.(Trp151Ter) variant in a single copy of the 7-dehydrocholesterol reductase *DHCR7* OMIM 602858 gene; the latter finding did not play any significant role in the analyzed case due to the autosomal recessive inheritance mode of the Smith-Lemli-Opitz syndrome which results from a homozygotic

* KBG syndrome is a rare genetic disorder characterized by distinctive facial features, skeletal abnormalities, intellectual disability, and developmental delay. It is caused by mutations in the *ANKRD11* gene. The syndrome is named after the initials of the first letters of the surnames of three families described with the condition in 1975.

mutation or possibly a complex heterozygote of the aforementioned gene. The above results confirmed the clinical diagnosis of the ID syndrome with facial dysmorphia due to a pathological mutation of the *SETD5* gene which is responsible for MRD23 with the autosomal dominant inheritance pattern (Figures 3–6).

DISCUSSION

The gene variant is a variant of a nonsense mutation that is associated with the presence of a premature termination codon which in turn results in a loss of function of the protein encoded by the *SETD5* gene. The protein encoded by this gene is a chromatin regulator necessary at early stages of cerebral development: it regulates the rate of the RNA transcript formation, thus affecting the translation and finally proliferation of the neural stem cells, as well as the synaptic transmission. The loss of function of the *SETD5* gene results in abnormalities having the character of ID [4, 5]. This type of mutation is rare, yet its character is evidently pathogenic and thus it may be responsible for the clinical features observed in the boy. Patients with the *SETD5* gene mutation have not been described as suffering from growth deficiency; however, the growth pattern observed in the presented patient shows a deviation noted in the prenatal period being below the 3rd centile, i.e. below the value equal to two standard deviation values as compared to the MPH. The phenomenon cannot be explained by GH deficiency; also the birth body mass of the patient does not meet the criteria of diagnosing small for gestational age body mass (SGA). Absorption disorders and other hormonal disorders that could impair the growth and development of the child were excluded. The boy is under long-term endocrinological follow-up aiming at controlling his growth and insulin-like growth factor I OMIM 147440 (IGF1) concentration values, as well as at providing the hormonal assessment of his hypothalamic-pituitary-adrenal axis and puberty level.

The coordinated tissue-specific regulation of gene expression is necessary for the appropriate development and harmonious functioning of all the systems. Mutations in numerous transcription regulators result in a group of neurodevelopmental disorders (NDD) referred to as transcriptomopathies, which share similar properties involving abnormalities of the morphological structure, including facial dysmorphia with varying individual phenotypes, growth and development retardation accompanied by intellectual disabilities showing varying degrees of intensity. An example is the Cornelia de Lange syndrome, which is within the above class of aberrations and is caused by abnormalities encountered in various subunits or regulators of the cohesin complex. The identified mutations affect the methyltransferase-encoding *KMT2A* and *SETD5* genes, as well as various subunits of the chromatin-remodeling SWI/SNF complex [6].

Publications are available that describe intragenic mutations in the *SETD5* gene which are characterized by an overlapping but unique phenotype as compared to the 3p25 microdeletion syndromes [7]. This observation indicates that mutations involving various chromatin-associated factors cause overlapping of clinical phenotypes, thus emphasizing the fact of genetic heterogeneity that should be taken into consideration while performing the assessment of a clinical and molecular diagnosis of neurodevelopmental syndromes [8].

Similar conclusions may be found in a paper that presents the analysis of patients suspected of suffering from the KBG syndrome. Three subjects initially clinically diagnosed as the KBG syndrome were subjected to genetic testing (high resolution comparative genomic hybridization) and also to whole exome sequencing (WES). The tests allowed for identifying a *de novo* 116 kb deletion partially involving *SETD5*, as well as a mutation of two variants with a frameshift that also developed *de novo* in the *SETD5* gene. The results of the clinical reevaluation of the patients were in agreement both with the molecular findings and the primarily suspected KBG syndrome in view of the overlapping phenotype properties of KBGS and MRD23 [9, 10]. The suspicion of the KBG syndrome represented the initial diagnosis of the described patients, similarly as it happened in the case of the currently presented boy; nevertheless, the genetic analysis that was based on the NGS method confirmed the *SETD5* haploinsufficiency.

Chromatin-modifying disorders include a constantly growing group of NDD which result from mutations in the functionally related chromatin genes. Such syndromes are characterized by a significant degree of phenotype overlapping since they share some common clinical features, including intellectual disability, developmental retardation, growth retardation and a similar morphological facial phenotype. Although the KBG syndrome is functionally related to the group of NDD, it is not formally classified as a member of this group, while the autosomal dominant MRD23 is included in the said group [9, 10].

Children with short stature and dysmorphic features who receive GH therapy due to SGA or hypopituitarism should undergo genetic testing [11].

CONCLUSIONS

Chromatin-modifying disorders represent an extensive group of NDD with overlapping phenotypes, and this is why it cannot be excluded that the height deficiency in the presented boy is a result of the presence of the *SETD5* gene mutation.

Children presenting with dysmorphia, height deficit and developmental retardation require a thorough pediatric-endocrinological analysis including their genetic background – in numerous cases, sequencing the entire exome using the NGS/WES method is indicated, or else

a comparative examination of the parental and offspring genomes (Trio-WES).

Establishing the diagnosis of a syndrome that results from a mutation of the *SETD5* gene requires multispecialist management followed by multi-profile rehabilitation, including an auxologic assessment, observation of the growing process and puberty, as well as the performance of hormonal tests, i.e. pediatric and endocrinological management.

All children with short stature and dysmorphic features or body proportion abnormalities who receive GH therapy require genetic testing.

DISCLOSURE

The authors declare no conflict of interest.

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