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CASE REPORT

SHORT syndrome in an 11-year-old boy – case report

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ABSTRACT

SHORT syndrome is a rare inherited autosomal-dominant disease. It has been clinically defined by its acronym: short stature, hyperextensibility of joints or hernia or both, ocular depression, Rieger abnormality, and teething delay. The prevalence of SHORT syndrome in the general population is still unknown. In this manuscript, we would like to present an 11-year-old boy with SHORT syndrome. He presented hypostature (121.3 cm) and low body weight (19.6 kg) in clinical examination. Furthermore, shortening of the forearm bones, incomplete teeth, and dysmorphia of the face (triangular-shaped face, prominent forehead, eye depression, narrow nose, slightly bent downwards, corners of the mouth directed downwards) were noticed. Molecular analysis of selected regions of the phosphatidylinositol 3 kinase-PIK3R1 gene showed the mutation Arg649Trp (R649W) in one allele of the *PIK3R1* gene (in a heterozygous system). The authors believe that this case report will draw attention to detecting the clinical features of SHORT syndrome, which allows for adequate diagnosis and treatment.

KEY WORDS:
children, PIK3R1 gene, rare disease, SHORT syndrome.

INTRODUCTION

In 1975, SHORT syndrome was described for the first time [1, 2]. SHORT syndrome is an autosomal dominant inherited, very rare genetic syndrome whose characteristic features are short stature, hyperextensibility of joints and/or hernias, ocular depression, Rieger anomaly and teething delay [3–5].

ABNORMALITIES OF PHENOTYPE

Frequent features of the SHORT syndrome are intrauterine growth restriction (IUGR) and slow weight and height gain. Morphology of the face in SHORT syndrome is also characteristic. Triangular-shaped face, prominent forehead, deeply set eyes, thin or underdeveloped nostrils (hypoplastic nasal wings), thin lips and mouth downturned, a small chin with a dimple, low-set ears, and wrinkles are often observed during examination [6]. Delayed bone age, excessive joint stretch, or thickening of the epiphyseal plate, as well as clinodactyly are malformations in the bone structure present in the course of the SHORT syndrome. Another typical feature of the syndrome is lipodystrophy. The loss of fat tissue is most often observed around the face, arms, and chest. It can also occur in the lumbar-sacral section of the spine and

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the buttocks area. Moreover, other disorders in the field of dentistry are also observed, namely small teeth (microdontia), reduced number of teeth (hypodontia), and enamel hypoplasia [6] (Table 1A).

ENDOCRINE DISORDERS

Endocrine disorders were a feature of several reports. Most of them concerned insulin resistance. There was a case of a 14-year-old girl with SHORT syndrome, who suffered from nonketotic hyperglycaemia and subsequently developed insulin resistance [7]. Later publications confirmed the association of insulin-resistant diabetes with the SHORT syndrome [8, 9]. Moreover, delayed menarche has been reported as a feature of this disease in female siblings [10] (Table 1B).

SENSE ORGANS DISABILITIES

Patients suffering from this syndrome often require a hearing aid due to the presence of sensorineural hearing loss.

Frequently, patients with SHORT syndrome present Rieger anomaly. It is the dysgenesis of the iris and cornea with marked hypoplasia of the iris stroma, displacement of the pupil (corectopia) and full thickness coloboma of the iris (pseudopolycoria). Schwalbe's line may be translocated into the anterior chamber of the eye. Consequently, higher ocular pressure can occur and in the future lead to glaucoma and vision loss [11] (Table 1C).

METABOLIC DISORDERS

Attention was also paid to abnormalities in calcium metabolism and nephrocalcinosis. Calcium deposition abnormalities are recorded in connection with the Rieger anomaly. There was a report of two sisters who, in addition to Rieger anomaly, had hydrocephalus, leptomeningeal calcifications, and mild intellectual disability. Both sisters had short stature, extensive anterior chamber pathology, and lost several teeth in early adulthood due to extensive caries. It was not determined whether the teeth eruption was normal or delayed [12]. In the course of SHORT syndrome, in two families the occurrence of renal stones was also reported [13] (Table 1D).

Differential diagnosis for SHORT syndrome includes several recognisable syndromes with short stature and similar facial features such as Russel-Silver or Floating-Harbor syndromes [14].

TABLE 1. SHORT syndrome features

A. Abnormalities of the body	Body proportion	Intrauterine growth restriction Delayed weight and height gain Lipodystrophy
	Face	Triangular-shaped face Prominent forehead Deeply set eyes Thin or underdeveloped nostrils (hypoplastic nasal alae) Thin lips and mouth downturned Small chin with a dimple Low-set ears Wrinkles
	Osteoarticular system	Delayed bone age Excessive joint stretch Thickening of the epiphyseal plate Clinodactyly
	Teeth	Small teeth (microdontia) Reduced number of teeth (hypodontia) Enamel hypoplasia
B. Endocrine disorders	Insulin resistance	
	Delayed menarche	
C. Sense organs disabilities	Hearing	Sensorineural hearing loss
	Eyesight	Rieger anomaly Glaucoma Vision loss
D. Metabolic disorders	Calcium metabolism	Nephrocalcinosis Leptomeningeal calcifications Extensive caries Renal stones

AIM OF THE STUDY

The aim of the manuscript is to describe the case of a boy with a rarely occurring genetically inherited SHORT syndrome and present the review of the available literature.

CASE REPORT

An 11-year-old boy was born in the 31st week of gestation, from the first pregnancy, by caesarean section due to intrauterine hypotrophy, unstable gestational diabetes, and myopia in the mother. On the Apgar scale, the boy was rated 6, 7, and 7 points in the 1st, 3rd, and 5th minutes, respectively. He showed features of IUGR. His birth weight was 1400 g (< 3rd percentile), body length was 43 cm (< 3rd percentile), and the head circumference was 25 cm (< 3rd percentile). After delivery, the boy underwent a surgery due to a giant inguinal hernia and bilateral cryptorchism. Echocardiography in the first year of life showed atrial septal defect (ASD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA).

During physical examination, short stature, low body weight, and slight shortening of the radius and ulna – bones of the forearm, were clearly noticed. His height (121.3 cm), weight (19.6 kg), and BMI (13.42 kg/m^2) remained below the 3rd percentile (Fig. 1). Value of the standard deviation score (height SDS – HSDS) in each of the measurements was < –2.0, which additionally spoke for the diagnosis of the boy's hypostature (Table 2).

Characteristic dysmorphic features, including triangle-shaped face, sharp facial features, disproportionately large head circumference, broad forehead, hypertelorism, depression of eyeballs, divergent and narrow nose, slightly bent downwards, large pinnae, broad oral fissure and narrow lips, and relatively wide neck, were also found. The boy's facial skin was dry and slightly wrinkled, similar to those with progeria (Fig. 2).

During the examination of the oral cavity, incomplete teeth and significant tooth decay were observed.

During several hospitalisations, the boy underwent profound diagnosis, which revealed the presence of some additional features of SHORT syndrome.

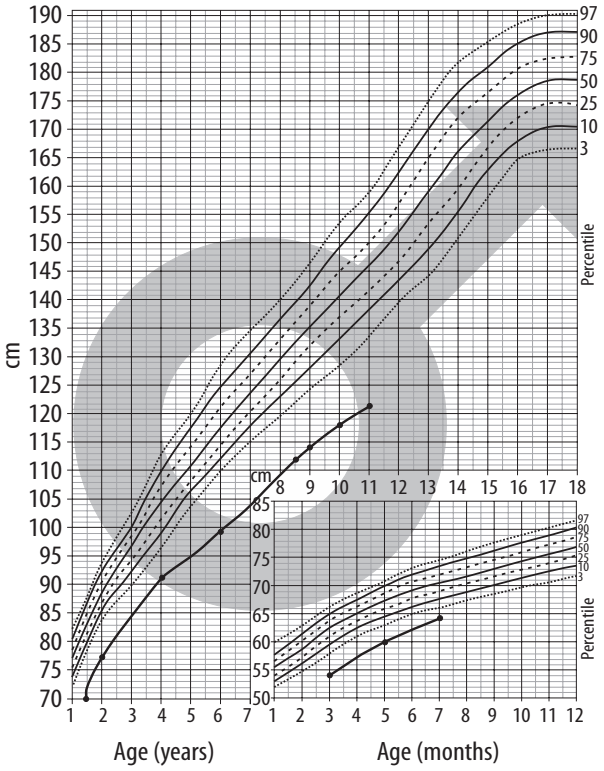

FIGURE 1. Growth curve on a growth percentile chart for Warsaw boys [21]

FIGURE 2. Our patient

TABLE 2. Height standard deviation score (HSDS) – value

Age	HSDS
3 months	–4
5 months	–3.5
7 months	–2.89
18 months	–5
2 years	–4.4
4 years	–3.47
6 years	–4.63
8.5 years	–3.71
9 years	–3.75
10 years	–3.75
11 years	–4.08

In an X-ray of the wrist with determination of bone age, performed in November 2017 (in the age of 9 years and 3 months):

- the distal ossification of the distal epithelial bone root was not shown (normally it appears at the age of 6 years),
- the nucleus of ossification of the trapezius major bone was poorly visible (normally it appears at the age of 4 years and 6 months),
- a weakly developed scaphoid bone was seen (characteristic for a 6-year-old child).

In June 2019 (at the age of 10 years and 10 months) an X-ray was performed once again. The bone age in this examination was estimated at 7–8 years.

The results of endocrine system evaluation, metabolic tests, and daily urine collection are presented in Table 3.

The profile of nocturnal growth hormone secretion, done in euthyreosis (twice in 2017 and 2019), was correct. IGF-1 serum concentration was also appropriate. On the basis of an oral glucose load test, an abnormal glucose tolerance was detected at the HOMA IR index of 2.46 and proper HbA1c concentration. Therefore, despite meeting auxological criteria, in the lack of literature evidence, it was not decided to treat the boy with a growth hormone treatment program for children who are small for gestational age (SGA). The ultrasound examination of the thyroid gland showed no significant abnormalities. During the abdominal

TABLE 3. Laboratory tests – results

Diagnostic test		Hospitalisation 2017	Hospitalisation 2019	Reference ranges
Blood tests				
Thyroid-stimulating hormone – TSH (µl/U/ml)		1.28	1.35	0.27–4.2
Free thyroxine – fT4 (ng/dl)		1.12	1.09	0.93–1.7
Parathormone (PTH) (pg/ml)		31.16	26.9	15–65
Insulin (µU/ml)	0′	3.89	10.98	2.6–24.9
	120′	208.8	122.8	
Glucose (mg/dl)	0′	87.2	90.9	60–99
	120′	153.5	152.4	
Glycated haemoglobin – HbA1c (%)		–	5.414	4.0–6.0
Growth hormone – GH (ng/ml)	I	17.3	23.84	–
	II	7.26	18.21	
	III	2.96	7.82	
	IV	2.23	15.15	
	V	5.02	10.97	
Ionised calcium (mmol/l)		1.14	0.98	1.1–1.35
Total calcium (mmol/l)		2.44	2.29	2.2–2.7
Vitamin D – total (ng/ml)		18.76	26.65	30.0–80.0
Total cholesterol (mmol/l)		3.73	3.41	3.0–5.0
High-density lipoprotein cholesterol – HDL (mmol/l)		1.54	1.09	> 1.0
Low-density lipoprotein cholesterol – LDL (mmol/l)		1.93	1.91	–
Triglycerides (mmol/l)		0.57	0.9	≤ 1.7
IGF-1 (ng/ml)		–	180.8	117–305
Daily urine collection				
		Excretion		Reference ranges
Creatinine (mg/kg/24 h)		38.43		5–25
Uric acid (mg/kg/24 h)		13.45		≤ 12
Urea (mg/kg/24 h)		539.97		> 300
Mg (mg/kg/24 h)		5.53		≤ 2
P (mg/kg/24 h)		27.75		15–25
Ca (mg/kg/24 h)		6.65		1–4
Na (mmol/kg/24 h)		6.15		1–4
K (mmol/kg/24 h)		2.43		1–2

ultrasound examination in both kidneys hyperechogenic peripheral parts of pyramids were bilaterally described – features of nephrocalcinosis (Hoyer's grade Ib).

Daily urine collection showed high calcium, uric acid, magnesium, and sodium excretion (Table 3).

The boy was also analysed for body composition, using bioelectrical impedance analysis (BIA), which showed a low amount of body fat and diminished E/I index (0.65) (Table 4).

In April 2016, molecular analysis of selected regions of the *PIK3R1* gene showed the mutation Arg649Trp (R649W) in one allele of the *PIK3R1* gene (in a heterozygous system). That research was performed by MedGen Medical Centre, Warsaw, Poland.

The boy is currently attending the fifth grade of primary school and is achieving good school performance. In the opinion of a psychologist, it was emphasised that the boy's general intellectual ability is at an above average level of intelligence. Word-conceptual skills are less developed than executive skills. He remains under regular, multi-specialistic care.

The boy's mother also suffers from SHORT syndrome. Molecular analysis of selected regions of the *PIK3R1* gene showed the same mutation as in her son. She is strikingly similar to her son in terms of phenotypes. Her weight is 43.4 kg, and height 147.3 cm, which corresponds to severe hypostature.

TABLE 4. Bioelectrical impedance analysis (BIA)

Parameter	Result
Lean tissue mass – LTM (kg)	17.3 (89.4%)
Fat mass compartment – FM (kg)	1.8 (9.2%)
Adipose tissue mass – ATM (kg)	2.4
Estimated body cell mass – BCM (kg)	9.7
Total body water – TBW (l)	12.2
Extracellular water compartment – ECV (l)	4.8
Intracellular water compartment – ICW (l)	7.4
E/I	0.65 (↓)

DISCUSSION

The prevalence of SHORT syndrome in the general population is still unknown. So far, several dozen cases have been described around the world [15, 16].

This supports the statement that this condition is rare in clinical practice. Nevertheless, knowledge of this disease is necessary during differential diagnosis, especially of other genetic syndromes. Paediatricians should take a close look at the patient's overall phenotype, particularly among children with hypostature. Many reports described an association between the occurrence of IUGR and short stature, low body weight, inguinal hernia, or hyperextension of joints and the characteristic facial dysmorphia in SHORT syndrome. Several manuscripts also document the coexistence of insulin resistance. It is generally accepted that intellectual development is normal. All these features refer also to the patient we have presented in this manuscript. In addition, in the course of SHORT syndrome, variable defects of the anterior chamber of the eye were described.

Patients with SHORT syndrome should remain under complex care. Systematic monitoring of the abnormalities can protect the patient from long-term consequences. From infancy, children should be examined for evaluation of the cardiac system due to the high risk of heart malformations. Furthermore, because of hearing loss related to this disease, it is vital to pay attention to speech development. It is also necessary to follow kidney function and calciuria and periodically perform kidney ultrasound to prevent nephrocalcinosis.

Despite published reports, the clinical criteria for the diagnosis of SHORT have not yet been determined. The main features described in the SHORT acronym are not found in every patient. What is more, the acronym does not include three cardinal clinical features of the condition, which are: facial dysmorphia, insulin resistance, and subcutaneous lipoatrophy. The patient's clinical picture can only suggest a disease, but the final diagnosis of the syndrome is made on the basis of molecular research.

The phosphatidylinositol 3 kinase (PI3K) pathway regulates fundamental cellular processes such as cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking. A central component in this pathway is the p85a regulatory subunit, encoded by *PIK3R1*. In 14 families with SHORT syndrome, a heterozygous mutation was recently detected in *PIK3R1* encoding the PI3K regulatory subunit [3, 17, 18]. What is more, a single sense change mutation (c.1945C> T; p.Arg649Trp) was found in eight families and apparently represents a mutational hotspot in this gene [5]. Identification of the gene responsible for the SHORT syndrome shows that short stature and low body weight, lipodystrophy and insulin resistance are the dominant symptoms of the disease [3, 17, 18]. Mutations of *PIK3R1* are probably responsible for variation of the downregulation of the Akt/mTor pathway [3, 17, 18], which could explain the presence of those characteristic symptoms. So far, 10 mutations evidently associated with SHORT syndrome have been described. The last of them – variant c.1956dupT (p.Lys653*) in exon 15 – was described in 2017 [6].

In our patient, Arg649Trp mutation (R649W) occurred in one allele of the *PIK3R1* gene (in a heterozygous system), which is already registered in the HGMD mutation database for the *PIK3R1* gene and is correlated with the clinical symptoms of SHORT syndrome. It consists of a heterozygous C> T de novo transition at the P653R1 coding position 1945. This conversion results in a change from arginine to tryptophan at position 649 of the mature protein. This mutation has also been described in previous reports [3, 5, 17–20].

CONCLUSIONS

Patients with mild clinical features of SHORT syndrome may not be sufficiently diagnosed and treated. We believe that our report will draw the attention of physicians to consider the SHORT syndrome in patients with hypostature, lipodystrophy, insulin resistance, and characteristic face dysmorphia.

DISCLOSURE

The authors declare no conflict of interest.

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