

SHORT Syndrome. Rare Genetic Condition

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Abstract

SHORT syndrome is a rare inherited condition and incidence of patients is unknown. Multiple anomalies (acronym SHORT) whose name stands for short stature, hyperextensibility of joints, ocular depression, Rieger anomaly and teething delay which are the main manifestations of the disease. The diagnosis of SHORT syndrome is based on physical findings, X-rays, and molecular genetic testing. The aim was to present a case extremely rare genetic condition characterised by short stature, dysmorphic features. Our patient shows most common signs and symptoms of SHORT syndrome except Rieger anomaly, lipodystrophy, hyper extensibility of joints. Such anomaly is considered as typical (element of set of symptoms listed in acronym SHORT) but not necessary to diagnose such syndrome.

Keywords: Short stature; Hyperextensibility of joints; Ocular depression; Rieger anomaly; Teething delay

Introduction

SHORT syndrome is a rare inherited condition in which affected individuals have multiple birth defects in different organ systems. SHORT syndrome prevalence is unknown. The frequency remains unknown (<1: 1000000) and less than 50 cases have been reported worldwide [1]. SHORT syndrome was first described in 1975 by Gorlin et al. in based on the physical features of two infants born to normal parents [2]. Multiple anomalies (acronym SHORT) whose name stands for short stature, hyperextensibility of joints, ocular depression, Rieger anomaly and teething delay which are the main manifestations of the disease [3].

Individuals with SHORT syndrome often display mild intrauterine growth restriction and gain weight slowly in childhood. Mild short stature has been seen in most adults reported to date. The height of molecularly confirmed diagnosis of SHORT syndrome in adult males was between 155 and 163 cm and in females between 143 and 160 cm [4-6]. Affected individuals often have additional features of the face include triangular shaped face, prominent forehead, deeply-set eyes, thin or underdeveloped nostrils (hypoplastic nasal alae), thin lips and mouth downturned, a small chin with a dimple, low-set ears, wrinkles [3,7]. Head shape usually is normal and occipital-frontal circumference is proportionate with other growth parameters.

Another typical feature of the syndrome is lipodystrophy which is a lack of fatty tissue under the skin, primarily in the face, arms, and chest. Insufficiency of the adipose tissue makes the blood vessels more visible through the thin and translucent skin [8]. The patients who suffer from the syndrome look much older than their calendar age shows, and the appearance of premature aging is referred to as progeria. The patients with SHORT syndrome have underdeveloped anterior chamber of the eye which is called Rieger anomaly. The syndrome also comprises dental abnormalities such as delayed tooth eruption, small teeth (microdontia), decreased number of teeth (hypodontia) [9,10]. Due to insulin resistance Individuals with SHORT syndrome may also develop diabetes in the second decade of life [8].

SHORT syndrome is inherited in an autosomal dominant manner, which means that one copy of the altered gene *PIK3R1* is sufficient to develop the disorder. In most cases, *de novo* mutation is found. It can be transmitted by one of the parents who has got the defected gene. More recently several research groups have identified *PIK3R1* mutations as responsible for SHORT syndrome [11]. *PIK3R1* gene (phosphoinositide-3-kinase regulatory subunit 1) located on chromosome 5 (5q13.1) that is on the long arm of chromosome 5 with the position 5q13.1. The

phosphatidylinositol 3 kinase (PI3K) signaling pathway is central to the action of many hormones and growth factors, including insulin, and is essential for differentiation of preadipocytes to adipocytes [12,13]. PI3K signaling is involved in many cellular functions such as growth, proliferation, migration, metabolism, survival and apoptosis. The diagnosis of SHORT syndrome is based on physical findings, X-rays, and molecular genetic testing. The aim was to present a case extremely rare genetic condition characterized by short stature and dysmorphic features.

Case Report

A 23-month-old boy was referred to our hospital with a history of poor growth. The child of the 1st pregnancy of non-consanguineous parents, proceeding with toxicosis during the 1st half. The boy was delivered at 33 weeks of gestation by the Cesarean section due to placenta failure with evidence of intrauterine growth restriction. The patient was born with a birth weight of 2100 grams (>3 percentile) and birth length of 44 cm (>3 percentile). Breastfed started at 5 days of birth. At 13-day boy was discharged from hospital with a general good condition and he gained the weight (2350 g). There is no known prior case with similar appearance in his family. At the age of seven months hearing loss was detected and the infant was treated for sensorineural hearing loss. At the age of the 9 month he had a hearing aid placed. He was able to sit at 7 months and started to walk at the age of 11 month. Eruption of first teeth was at the age of 14 month. Clinical examination showed that there was proportional stunting. At admission height was 77 cm, height SDS (-2.47), weight 8.3 kg, weight SDS (-3.59), head circumference was 48 cm (SDS-0.7). It was detected some dysmorphic features such as triangular-shaped face, prominent forehead, deeply set eyes, micrognathia. Evaluation revealed thin built with progeroid facies with loss of subcutaneous fat mainly in face, trunk and shoulders, maxillary hypoplasia and dimpled chin (Figures 1-3). His psychomotor development was had been normal but punctuated a little delay in acquisition of speech. Based on the dysmorphic features (triangular-

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Figure 1: Dysmorphic features with triangular-shaped face with prominent forehead and deeply set eyes.

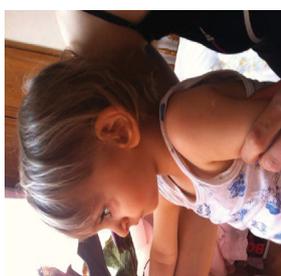


Figure 2: Micrognathia.



Figure 3: Loss of subcutaneous fat with vessels transparently.

shaped face, prominent forehead, deeply set eyes, micrognathia), short stature, sensorineural hearing loss SHORT syndrome was suggested. Tests for thyroid function, hormones of pituitary axis, insulin intolerance and calcium metabolism were done and reveal no pathology. X-Ray of left wrist detected a lightly delay of bone age.

To verify the diagnosis we performing molecular genetic testing and found a mutation in *PIK3R1*-variant c.1945C>T; p.Arg649Trp *de novo* (not present in biological parents) which is responsible for the symptoms in the patient.

Discussion

The diagnosis of SHORT syndrome is made on the basis of

molecular examination and clinical features. Our patient shows most common signs and symptoms of SHORT syndrome except Rieger anomaly, lipodystrophy, hyper extensibility of joints. Such anomaly is considered as typical (element of set of symptoms listed in acronym SHORT) but not necessary to diagnose such syndrome. The date of literature shows that major features described in the SHORT acronym are not universally seen and only half of affected people have 4 or more of the classic features [14].

Conclusion

Our case reported that the diversity of the clinical picture may largely depend on the type of mutation and the localization of the genetic defect [6]. Given the high risk of diabetes mellitus, regular monitoring of glucose metabolism is warranted. An echocardiogram, ophthalmological and hearing assessments are also recommended.

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