CASE REPORT

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SHORT SYNDROME: AN END TO THE DIAGNOSTIC ODYSSEY

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ABSTRACT

SHORT Syndrome is a rare genetic condition with less than 50 cases reported worldwide. Its name is an acronym, represented by Short stature, Hyperextensibility of joints, Ocular depression, Rieger anomaly and Teething delay. Other associated features include intrauterine growth restriction, lipodystrophy, delayed bone age and progeroid appearance. Cognitive function is usually preserved. Our patient was a 7-year-old-boy, referred at 9 months old for sex chromosome mosaicism detected on his karyotype analysis. He was born term via normal vaginal delivery with a birth weight of 2.05 kg and good Apgar score. Antenatally, mother was diagnosed with diabetes mellitus not requiring insulin. From 7 months gestation, serial scans showed symmetrical intrauterine growth restriction (IUGR). Examination at birth revealed a baby small for age, with prominent ears and micrognathia. During his subsequent clinic visits, he manifested Russell-Silver-like phenotype; failure to thrive, broad forehead and triangular facies, although additional features of wrinkled skin over his hands and feet, deep set eyes, groove over his chin and large ears were also seen. Genetic studies for Russell-Silver Syndrome (RSS) and chromosomal microarray testing which was done subsequently, were both normal. His genetic condition remained elusive for many years. A clinical diagnosis of SHORT Syndrome was finally considered. Polymerase Chain Reaction (PCR) and direct sequencing method was used to analyse the targeted gene at Institute for Medical Research (IMR), Kuala Lumpur. A heterozygous mutation was detected at c.1945C>T in exon 15 of *PIK3R1* gene; which impairs cellular growth and proliferation. This case report discusses the differential diagnosis of a dysmorphic child with short stature with RSS-like phenotype.

Keywords: Short stature, dysmorphism, genetic testing, accurate counselling

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Introduction

SHORT Syndrome was first introduced by Gorlin et al. in 1975 and since then, very few cases have been reported worldwide [1]. The prevalence of the disorder is unknown [2]. The acronym SHORT defines a recognizable pattern of features, consisting of Short Stature, Hyperextensibility of joints and/or inguinal Hernia, Ocular depression, Rieger anomaly, and Teething delay. Other findings include mild IUGR; partial lipodystrophy (evident at birth in the face, and later in the chest and upper extremities, often sparing the buttocks and legs); and a characteristic facial gestalt. Other frequent features include: insulin resistance (typically in mid-childhood to adolescence) and/or diabetes mellitus in early

adulthood; and sensorineural hearing loss [1,2]. To date, the diagnosis has been molecularly confirmed in individuals from <50 families [1]. The current understanding of the phenotypic spectrum and natural history are likely to evolve over time.

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Case history

MI was first referred to us at the age of 9 months old for an abnormal karyotype. He was delivered full term via normal vaginal delivery with a birth weight of 2.05 kg. Antenatally, mother was diagnosed with gestational diabetes mellitus during first trimester and had good sugar control throughout her pregnancy. Late antenatal scans showed intrauterine growth restriction. He was a second child from a non-consanguineous marriage. The dysmorphic features were seen at birth include triangular facies, prominent ears and micrognathia, with normal male genitalia and with bilaterally descended testes. A chromosomal study was sent, which showed a mosaic pattern of 45,X/46,XY cell line. Echocardiogram and renal ultrasound studies to assess cardiac, aortic, and kidney structures were all normal. Genetic counseling on Mosaic Intersex Syndrome was appropriately given to both parents [8].

During his subsequent clinic reviews, his growth parameters started falling off centiles and his dysmorphic features became more distinct and of which not typically seen in Mosaic Intersex Syndrome [7,8]. He had sparse hair, prominent, broad forehead, triangular facies, deep set eyes, large ears and a groove was noted at his chin. He had wrinkled skin over his hands and feet and his joints were not lax. He had delayed tooth eruption at 14 months old. A second pathology was considered at this point as the phenotype was not fully explained by the karyotype findings. In view of some overlapping features with Russell-Silver

Syndrome [9] and as per recommendation [12], methylation testing, uniparental disomy and Single Nucleotide Polymorphism (SNP) microarray analysis were performed; which turned out to be negative. Whole Exome Sequencing (WES) was not available locally and testing cost overseas was an issue. We continued to monitor his development, which has remained relatively normal till now and referred him to a dietitian for calorie optimization. At this point, parents were informed that the abnormal karyotype findings did not fully explain the dysmorphism seen in him [7] and a dual pathology was being considered.

Expert opinion from overseas was sought, however his diagnosis remained unknown till he was 5 years old and SHORT syndrome was finally considered after extensive literature and dysmorphology search. Single gene sequencing of *PIK3R1* gene was performed at IMR confirmed his diagnosis of SHORT Syndrome.

Characteristic facial gestalt (A-C). The face has a triangular appearance. The forehead is prominent and the eyes are deep-set. The nose has a narrow tip and thin nasal alae. The columella is low-hanging. The middle and lower thirds of the face is relatively small. The corners of the mouth are downturned and the chin is dimpled. The ears are prominent but often not low set. There is lack of fatty tissue under the skin (E and F). This lack of fat, together with thin, wrinkled skin and visible veins beneath the skin, make affected individuals look older than their biological age. This appearance of premature aging is sometimes described as progeroid. Partial lipodystrophy is universal in SHORT syndrome. Lack of subcutaneous fat is evident in the face and later becomes more readily apparent in the chest and upper extremities. Growth chart (G and H) Patient's height falls within his midparental range. Patients with SHORT syndrome usually have less pronounced short stature.

Genetic analysis

To verify the patient's diagnosis, we went ahead and performed molecular genetic testing. Genomic DNA was extracted from whole blood by using a DNA isolation kit (Perkin Elmer) according to manufacturer's instruction. PCR was carried out to amplify all 15 exons of *PIK3R1* gene including splice

sites. The PCR products were then sequenced using BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems) in order to look for sequence variant. Several in silico analysis were performed to assess the impact of the variant detected.

Heterozygous missense mutation was identified at c.1945C>T p(Arg649Trp) in exon 15 of *PIK3R1* gene. This mutation has been reported in Human Gene Mutation Database (HGMD) for SHORT Syndrome by Dymet et al. (2013). Parental analysis that was performed subsequently were both normal and hence the de novo pattern of inheritance in this family.

Discussion

SHORT syndrome is a rare genetic condition worldwide [1,2]. It was first described by RJ Gorlin et al. in 1975 [10] based on the striking physical features of two brothers born to normal parents. Over time, few more affected individuals have been described and the clinical definition of SHORT syndrome was further elucidated [4]. The word SHORT represents the findings in an affected person: (S) = short stature, (H) = hyperextensibility of joints and/or inguinal hernia, (O) = ocular depression, (R) = Rieger anomaly, (T) = teething delay.

Not all of these features are required for a diagnosis of SHORT syndrome [1,2]. Interestingly, facial gestalt in SHORT syndrome seems to be a consistent feature- triangular appearance of the face, prominent forehead, deep-set eyes, narrow tip of the nose and low-hanging columella. The middle and lower thirds of the face is relatively small; the corners of the mouth are downturned and the chin is dimpled; the ears are prominent but often not low set [1].

Lipodystrophy is also commonly seen, causing difficulty gaining weight. This typically presents first in the face followed by the chest and upper extremities in the first few years of development. Often, the lower extremities are spared from lipodystrophy, but overall body appearance is thin with low body mass index (BMI). Some affected individuals have speech delay and other developmental delays but intelligence is usually normal. Insulin resistance is common in mid-childhood to adolescence, often progressing into diabetes mellitus by early adulthood. Babies with SHORT syndrome are usually born at or slightly before term, but often have low birth weight, small head circumference, and shortened length. Individuals with SHORT syndrome are thought to have a normal life-expectancy [2].

Differential diagnosis of SHORT syndrome will include Rieger syndrome, Russell-Silver syndrome, Alagille syndrome, Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) and Hutchinson-Gilford progeria syndrome [1].

To date, less than 50 *PIK3R1* mutations have been reported in HGMD which consist of missense mutations, small deletions and small insertions [3,4,5]. *PIK3R1* gene is localized at chromosome 5 and plays a significant role in the metabolic actions of insulin, and a mutation in this gene is known to be

associated with insulin resistance [3]. Mutation detected in our patient is the most prevalent mutation identified in SHORT Syndrome [3,4]. Winnay (2016) showed that the knock-in mouse have reduction in body length, systemic insulin resistance and reduced fat mass and Marie (2018) suggested that the c.1945C>T is important in glucose and adipose tissue metabolism. Although Marie et al. (2017) demonstrated that knock-in mouse with this mutation has abnormal development of the iris and anterior segment dysgenesis, this symptom was not observed in our patient.

Causes

SHORT syndrome is caused by mutations in the *PIK3R1* gene. This gene is responsible for proper production of the enzyme PI3K that is involved in many cell activities including cell growth and division, transport of materials within cells, movement of cells, and regulation of the hormone insulin [3,6].

Inheritance

SHORT syndrome is inherited in an autosomal dominant manner, when only a single copy of an abnormal gene is necessary to cause a particular disease. Most cases of SHORT syndrome are de novo in origin. Risk for future offspring in unaffected parents is low [1,2] Our family received detailed genetic counselling encompassing the natural history of the disorder itself, its inheritance pattern and recurrence risk which is low in this family (small risk of gonadal mosaicism cannot be ruled out). Pre- and post- test genetic counselling was performed prior to all genetic analysis for this family.

Affected populations

SHORT syndrome is a very rare disorder with fewer than 50 reported cases in the literature to date [1,2]. SHORT syndrome is not known to be more prevalent in a certain ethnic group or geographic location [1]. To the best of our knowledge, this is the first reported case of molecularly confirmed SHORT Syndrome from Malaysia.

Standard therapies and long term management

No specific treatment exists for SHORT syndrome; supportive therapy is individualised, on a case-by-case basis. Rieger anomaly/glaucoma, dental anomalies, insulin resistance/diabetes mellitus and hearing loss can often be treated by appropriate

medical specialists. Given the increased risk for insulin resistance, it is generally advisable to avoid growth hormone treatment [1]. Our patient has a regular monitoring of his growth including height, weight, and body mass index. He has multiple follow up appointments with relevant specialties. His initial eye and hearing assessment, echocardiogram and ultrasound kidneys were all normal. He is planned for insulin resistance and diabetes monitoring from 10 years onwards [1]. He is currently attending mainstream school and has no learning issues.

Conclusion

SHORT Syndrome should be included as a differential diagnosis for patients with a possible diagnosis of Russell-Silver Syndrome, Progeria and Lipodystrophy, due to their overlapping clinical features. Early diagnosis enables accurate genetic counselling with proper long term monitoring and surveillance plan in place.

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