A de novo TBX3 mutation presenting as dorsalization of the little fingers: A forme fruste phenotype of ulnar-mammary syndrome

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\textbf{A B S T R A C T}

Ulno-mammary syndrome (UMS) is a rare syndromic limb malformation caused by heterozygous mutations in TBX3. The name highlights the two commonly involved body parts i.e. mammary gland and ulnar ray of the upper limbs, although a more extensive systemic involvement is also known to occur. Here, we report the surprising finding of a patient with a de novo mutation in TBX3 whose clinical presentation is limited to dorsalization of both little fingers and slightly deep 4th web spaces. We review the literature to confirm that this should be considered as a forme fruste phenotype of UMS.

1. Introduction

Ulnar-mammary syndrome (UMS; OMIM: 181450) is a rare syndrome caused by heterozygous mutations in TBX3 (Schinzel, 1987; Bamshad et al., 1997). The clinical presentation is known to be variable among affected family members. The two main characteristic features are mammary gland defects (such as absent/hypoplastic breasts, and nipple/areola abnormalities) and ulnar-sided upper limb defects which may present with “stiff hypoplastic little fingers”, postaxial polydactyly, or hypoplasia/aplasia of the ulnar digits/ulna. Other features include apocrine sweat gland defects, short stature, hypogonadism, pituitary gland abnormalities, hypoplastic canines, pyloric stenosis, subglottic stenosis, laryngeal webs, anal defects, and cardiac defects (Bamshad et al., 1999; Linden et al., 2009).

The term “stiff hypoplastic little fingers” as a feature of UMS was mentioned in old and recent publications (Hecht and Scott, 1984; Bamshad et al., 1999; Wollnik et al., 2002; Tanteles et al., 2017). We reviewed the illustrations of these cases and found that all illustrated cases had dorsalization of the palmar skin (i.e. the palmar skin is hyperpigmented with loss of the normal palmar glabrous skin appearance) of the little finger with or without ulnar-sided cleft hand. Dorsalization of the palmar skin of the little finger is known in the Hand Surgery literature as “distal dorsal dimelia” and is defined as the appearance of dorsal structures (such as skin hyper-pigmentation or the presence of a nail) on the palmar aspect of the digits (Al-Qattan et al., 2010; Al-Qattan, 2013). Dorsalization of the little finger is frequently associated with loss of flexion as well as a deep cleft at the 4th web space which is known as “ulnar-sided cleft hand” malformation in order to differentiate it from central hand clefts of split hand/feet malformation (Al-Qattan, 2014).

In this paper, we report on a patient with a de novo mutation in TBX3. The presentation was isolated bilateral dorsalization of the little fingers and slightly deep 4th web spaces. We review the literature to confirm that this should be considered as a forme fruste phenotype of UMS.

2. Clinical report

A 10-year-old girl presented to the hand clinic for assessment of stiffness of both little fingers. The parents are unrelated, had no abnormalities and had another heathy unaffected son. Except for the bilateral hand defects, clinical examination of the patient showed no abnormalities. Both breasts were staged as Tanner II and were appropriate for age. The external genitalia had no defects and pelvic ultrasound was normal. Both little fingers showed dorsalization of the palmar skin with absent proximal interphalangeal joint creases. The distal interphalangeal joint crease was faint on the right and absent on the left. There was slight deepening of both 4th web spaces (Fig. 1a and b). The left little finger had no active or passive flexion at both interphalangeal joints. The right little finger had no active or passive flexion at the proximal interphalangeal joint but had active flexion at the distal interphalangeal joint (Fig. 1c). Radiological examination of the limbs
showed no abnormalities except for the mild shortening of the little fingers (Fig. 1d). Ultrasound of the abdomen and echocardiogram showed no abnormalities.

Initially, the diagnosis of distal 4q deletion syndrome was suspected; but the analysis for 4q deletion syndrome was negative. Blood was taken from parents and both siblings for whole exome sequencing, but the analysis for 4q deletion syndrome was negative. The twin brothers had all the characteristic features of UMS. The father and his twin sons with UMS caused by a non-sense mutation of the TBX3 gene. The twin brothers had all the characteristic features of UMS. The father was completely normal except for bilateral dorsalization of the little fingers. The authors (Tanteles et al., 2017) described these deformities of the little fingers as hypoplasia of the distal phalanx of the left little finger and absent flexion creases of the right little finger. However, when we examined the illustrations, it was obvious that both little fingers also had dorsalization of the palmar skin. Our patient demonstrated the bilateral little finger defects and no other systemic abnormalities were noted. The Tanner breast staging was appropriate for age and there was no evidence of hypogonadism. However, mammary and apocrine glands have not yet reached maturity in our patient.

It is interesting to note that the UMS phenotype overlaps with the phenotype of HAND2 deletion (dorsalization of the little fingers and cardiac defects) (Vogt et al., 2006) as well as with the phenotype GLI3 mutations such as Pallister-Hall syndrome with regards to ulnar polydactyly, anal abnormalities and laryngeal defects. (Al-Qattan et al., 2017). These overlapping features may be explained by the well-known interactions between HAND2 and the expression of both GLI3 and TBX3 (Osterwalder et al., 2014).

In conclusion, we demonstrate that TBX3 mutations in UMS may present with isolated dorsalization of the little fingers. We also emphasize the use of the term “dorsalization” instead of ‘stiff’ or ‘hypoplastic’ little fingers in the description of the phenotype.

Conflicts of interest

There is no conflict of interest.

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