Say-Barber-Biesecker-Yong-Simpson syndrome (SBBYSS) or Ohdo Blepharophimosis syndrome : A first Tunisian case

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ABSTRACT

KAT6B disorders include Say-Barber-Young-Simpson of Ohdo syndrome (SBBYSS) and genitopatellar syndrome (GPS) which are part of a braod phenotypic spectrum with variable expressivity. We described the first case of a newborn boy, in whom a molecular study was performed and a heterozygous pathogenic variant was detected in the KAT6B (NM_012330.3) by DNA sequence analysis. It was a nonsense variant, c.5146C>T (p.(Gln1716*)) and this result confirm the diagnosis of Ohdo syndrome, SBBYSS variant. He had the particularity of presenting a complex laryngeal malformation, which has not been described in previous cases.

RÉSUMÉ

Le syndrome de Say-Barber-Young-Simpson, variante du syndrome d'Ohdo et le syndrome genitopatellaire, font partie d'unspectrephénotypique à expression variable des anomalies dans le gène KAT6B. Nous rapportons le cas d'un nouveau-né de sexemasculin, chez qui la biologiemoléculaire a confirmé le diagnostic de syndrome du syndrome de Say-Barber-Yong-Simpson. Une mutation non sens, c.5146C>T (p.(Gln1716*) a étédétectée chez lui à l'état heterozygote.Notre patient présente la particularitéphénotypiqued'uneanomaliecongénitalecomplexe du larynx, qui n'a pas étérapportéeauparavant dans la littérature.

INTRODUCTION

Dr ShozoOhdo from Japan first described a family in which 2 sibs and their cousin had blepharophimosis, ptosis, congenital heart defects, intellectual disability and hypoplasic teeth (1). Patients with similar features were reported by Young and Simpson, Say and Barber, and Biesecker (2, 3, 4). In 1988, Goldblatt et all described skeletal features, mental retardation, genital and renal anomalies, in a 4-year-old boy and named this condition as genitopatellar syndrome (GPS) (5). For many years, these conditions have been considered as separate entities (6). However, since 2011/2012, we know that Say-Barber-Yong-Simpson syndrome(SBBYSS) and genitopatellar syndrome (GPS) are two rare diseases caused by de novo heterozygous sequence variants in KAT6B gene (6).

CASE REPORT

A newborn boy, the first child of healthy but consanguineous parents was admitted in our department because of neonatal respiratory distress and multiple congenital anomalies. The patient was born at term, pregnancy was complicated by polyhydramnios of unknown aetiology. Birth weight was 3190 g (25th-50th centile), length was 52 cm (95th centile) and head circumference was 35 cm (50th centile). Facial findings included a round face, blepharophimosis, epicanthus, hypertelorism, low set ears, flat nose with a wide nasal bridge, a long flat philtrum,thin upper lip, thin lip vermilion, microretrognathia and cleft palate. He had the aspect of mask-like facies (Fig 1).

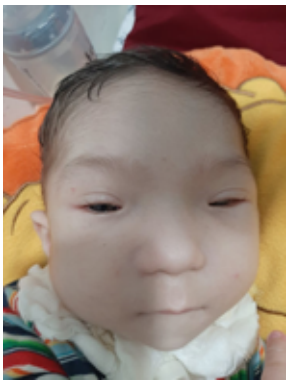

Figure 1 : blepharophimosis, epicanthus, hypertelorism, flat nose with a wide nasal bridge, a long flat philtrum, thin upper lip, thin lip vermilion and microretrognathia / aspect of mask-like facies.

He was managed by oxygen and antibiotic therapy, but he was dependent on oxygen; moreover, we noticed that our patient had a congenital stridor. He had a moderate hypotonia. There was scrotal hypoplasia and cryptorchidism. The hands showed proximally implanted thumbs. At the feet, he had long great toes and overlapping and underlapping toes (Fig 2).

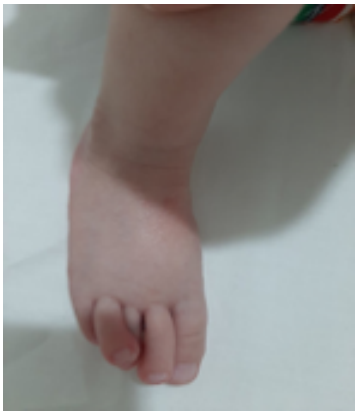

Figure 2 : long great toes and overlapping and underlapping toes.

No abnormalities of hair, ears, anal margin or skins had been observed. He was explored by rigid endoscopy and showed laryngomalacia with a posterior glottis stenosisand redundant supraglottic mucosa. Abdominal and renal ultrasound showed left pyelic ectasia. Testicular ultrasound showed left testicle intra-abdominal and the right one was in inguinal position. Echocardiography was normal and transfantanellar ultrasound highlighted a septum pellucidum cyst. Karyotype was normal (46 XY). He had congenital hypothyroidism and thyroid ultrasound was normal. He was operated on for his laryngomalacia and kept a tracheotomy. Currently, he is 6 months old; he has feeding difficulties with dependence on oxygen, his weight gain is bad and he has developmental delay. The diagnosis of Ohdo syndrome has been suspected. A molecular study was performed and a heterozygous pathogenic variant was detected in the KAT6B (NM_012330.3) by DNA sequence analysis. It was a nonsense variant, c.5146C>T (p.(Gln1716*)) and this result confirm the diagnosis of Ohdo syndrome, SBBYSS variant caused by a pathogenic variant in the KAT6B gene. Family members of the counselee may be at an increased risk of having above-mentioned autosomal dominant disorder. For each child, parent, brother or sister of the counselee, the a priori risk is 50% (with complete penetrance). The provision of genetic advice to the patient and family members may therefore be indicated.

DISCUSSION

KAT6B disorders include genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Yong-Simpson syndrome variant of Ohdo syndrome (SBBYSS) which are part of a broad phenotypic spectrum with variable expressivity; individuals presenting with a phenotype intermediate between GPS and SBBYSS have been reported (7).

The SBBYSS (MIN 603736) variant of Ohdo syndrome is a rare multiple congenital anomaly syndrome, which is usually diagnosed clinically on the basis of a striking facial phenotype (8). Clinical criteria for the diagnosis of SBBYSS [White et al 2003] have been expanded by the authors to prompt suspicion of SBBYSS. Individuals with two major features or one major feature and two minor features are likely to have a KAT6B disorder (7). Major features were long thumbs or great toes, immobile mask-like face, blepharophimosis, lachrymal duct anomalies and patellar hypoplasia or agenesis. Minor features were congenital heart defect, dental anomalies, hearing loss, thyroid anomalies, cleft palate, genital anomalies, hypotonia and global developmental delay (7). In our patient, there were 3 major features and 5 minor features. However, he had the particularity of presenting a complex laryngeal malformation, which has not been described in previous cases. In fact, only a few rare cases of laryngomalacia without anatomical involvement and with spontaneous resolution have been reported in the literature; moreover, laryngomalacia was described in a minority of GPS subjects (7). A stridor due to laryngomalacia resolved spontaneously, was described in one patient from 11, by Verloes et al (9) in his study on blepharophimosis mental retardation (BMR) syndrome;the diagnosis of Ohdo syndrome was proposed in this child. Campeau et al reported that mutations to the last exon, leading to reductions in protein levels (haploinsufficiency) lead to an SBBYSS phenotype; distal mutations in the last exon, which also give SBBYSS phenotype, may thus lead to a similar phenotype by a loss-of-function mechanism. Yet, some of the facial and digit features of SBBYSS are only seen in individuals with the most distal mutations (10). About genotype-phenotype correlations, SBBYSs-causing pathogenic variants also occur most frequently in exon 18, but more distally than the GPS-associated variants. Recently, predicted loss-of function variants in exons 3, 7, 11 and 14-17 were reported to be associated with SBBYSS phenotype (7). Whereas, most GPS-associated pathogenic variants cluster in KAT6B exon 18, the last exon, and are predicted to produce truncated proteins associated with a gain-of-function mechanism. Consistent with this hypothesis, pathogenic variants associated with more severe GPS phenotypes are located more proximally in exon 18 and are predicted to result in a more truncated protein (7). Despite these findings, the precise roles of KAT6B in regulating gene transcription during development have still to be defined. A better understanding of the phenotype resulting from KAT6B mutations may lead to insights into the molecular roles of *KAT6B*.

DISCUSSION

The prevalence of KAT6B disorders is not known, but is estimated at less than one in a million individuals. To date, 89 individuals with moleculary confirmed KAT6Bdisorders have been reported in the literature, including 18 with GPS, 58 with SBBYSS, and 13 described as having an intermediate phenotype. To our knowledge, our patient repre-

sents the first case with KAT6B disorders; its clinical features agree with the diagnosis of SBBYSS, even if he has atypical laryngeal malformations. The diagnosis of SBBYSS was moleculary confirmed and prenatal and the provision of genetic counseling at risk family members may be indicated.

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