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Title: First molecular diagnosed patient from Turkey with Townes-Brocks syndrome

Running title: A first reported patient with TBS from Turkey

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Abstract

Townes–Brocks syndrome (TBS) is a rare syndrome characterised by triad of anal, ear and thumb anomalies. Further malformations/anomalies include congenital heart diseases, foot malformations, sensorineural and/or conductive hearing impairment, genitourinary malformations, and anomalies of eye and nervous system. Definitive diagnosis for TBS is confirmed by molecular analysis for mutations in the *SALL1* gene. Only one known case of TBS with absent pulmonary valve syndrome has been previously described to our knowledge. Here, we report a newborn diagnosed of TBS with absent pulmonary valve syndrome and who was found to carry the most common pathogenic *SALL1* gene mutation c826C >T (pR276X).

Key words: Townes–Brocks syndrome, absent pulmonary valve syndrome, SALL1 gene, preaxial polydactyly, triphalangeal thumb.

Introduction

Townes–Brocks syndrome (TBS, OMIM #104780) is a rare autosomal dominantly inherited malformation syndrome characterised by triad of anal, ear and thumb anomalies. Other anomalies such as renal impairment with or without structural abnormalities, congenital heart diseases, foot malformations, genitourinary malformations, and sensorineural and/or conductive hearing impairment may occur. Rare eye anomalies can include iris coloboma, microphthalmia, and cataract. Central nervous system anomalies can include Duane anomaly, Arnold-Chiari malformation type 1, intellectual disability and behavioral problems. Growth retardation may also occur (1). The estimated prevalence of TBS in the general population is approximately 1 in 250,000 live births (2). Definitive diagnosis for TBS is confirmed by molecular analysis for mutations in the *SALL1* gene. The most common pathogenic variant is c.826C>T (p.Arg276Ter) and this mutation causes a severe phenotype in all known instances (1, 3).

We, herein, report a newborn diagnosed of TBS with severe congenital heart disease and who was found to be the pathogenic *SALL1* gene mutation c826C >T (pR276X).

Case report

A 2810 g singleton, female infant born to a 26-year-old mother from her second pregnancy via planned, repeated caesarean section at 39 weeks of gestation, was admitted to the neonatal intensive care unit due to tetralogy of Fallot (TOF) which was diagnosed antenatally. APGAR scores were 9 and 10 at 1 and 5 min, respectively. On admission her weight was 2810 g (10-50th percentile), the length was 49 cm (10-50th percentile) and the head circumference was 36 cm (50-90th percentile). She had non-consanguineous parents and 6 year old healthy brother. On physical examination, she had imperforate anus with rectoperineal fistula, microcephaly, Satyr's ear, mildly protruding dysplastic ears with overfolding of superior helices (Figure 1).

She had preaxial polydactyly on the right hand and triphalangeal thumb on the left hand, confirmed by X-Ray examination (Figure 2). The left foot had talipes equinovarus deformity. She had a grade 3/6 pansystolic murmur on cardiac auscultation at the mesocardiac region. Ophthalmological examination was normal for both eyes. An echocardiographic examination revealed absent pulmonary valve syndrome (APVS) with TOF and dilated pulmonary arteries. Cranial ultrasonography was unremarkable. Abdominal ultrasonography showed increased echogenicity of the renal parenchyma and mildly pelvicalyceal dilatation in both kidney. Serum creatinine level was 1.22 mg/dl at the third day of life and 1.11 mg/dl at the fourth day of life (normal range for serum creatinine level: 0.4-0.9 mg/dl). Thyroid profile showed free thyroxine of 15.6 pmol/mL (normal range: 12-22 pmol/mL) and thyroid-stimulating hormone of 4.9 μIU/L (normal range:1.7-9.1 μIU/L). Thyroid ultrasonography was normal. The brainstem evoked response audiometry test revealed bilateral sensorineural hearing loss.

The patient presented clonic seizure in right upper and right lower limbs on day 45 of life. Levetiracetam was initiated for treatment of seizure. Cranial ultrasonography of the same day was normal. Electroencephalography could not be performed due to the poor clinical condition of the patient.

In light of all these findings, the patient was clinically diagnosed with Townes-Brocks syndrome. As a result of the *SALL1* mutation analysis, a previously defined c.826 C> T pathogenic mutation was detected.

The patient was intubated due to respiratory distress and she was placed on mechanical ventilation on day 60 of life. A chest X-ray showed cardiomegaly. Computed tomography of the chest demonstrated enlarged right and left pulmonary arteries causing bilateral bronchial compression. Bronchoscopy which was performed before cardiac surgery showed occlusion of the bronchi.

The infant underwent surgery to repair of APVS with TOF and dilated pulmonary arteries on day 85 of life. The patient could not be extubated during the follow-up in the intensive care unit and she died in the 6th month of life due to pneumonia and sepsis.

Discussion

Townes and Brocks first described in 1972 an autosomal dominant malformation syndrome, now known as TBS, as an association of anal, hand, foot, and ear abnormalities (4). Bozal-Basterra et al (5) proposed that TBS is a potential ciliopathy-like disorder with symptoms caused by truncated SALL1 interfering with the normal function of cilia and/or centrosomal-related proteins. The diagnosis of TBS is made by evaluating the following major and minor criteria. Major criteria include imperforate anus or anal stenosis, dysplastic ears (overfolded superior helices, microtia), typical thumb malformations (preaxial polydactyly, triphalangeal thumbs, hypoplastic thumbs) without hypoplasia of the radius. Minor criteria include sensorineural and/or conductive hearing impairment, foot malformations (syndactyly, overlapping toes, missing toes, pes planus, club foot, fused metatarsals), renal impairment with or without renal malformations, genitourinary malformations, congenital heart disease. If the three major criteria are present, the diagnosis of TBS is made. If only two major criteria are present, the occurence of minor criteria without radius hypoplasia or cleft lip/palate further support the diagnosis (1, 6). Occasionally, imperforate anus with recto-perineal/recto-vaginal fistulas or anteriorly-placed anus may occur (7). Pre-auricular ear tags, lop ear may also be seen as external ear malformations (6). As our patient had three major criteria and most of the minor criteria of TBS, we diagnosed the patient with TBS.

Congenital heart defects may be seen in 50% of patients with the common R276X mutation and 12%-25% of patients with other SALL1 mutations. These heart defects include atrial septal defect, ventricular septal defect, TOF, truncus arteriosus, pulmonary valve atresia, and

persistent ductus arteriosus (1, 3, 7, 8). R276X mutation is the only SALL1 mutation known to be associated with TOF. Absent pulmonary valve syndrome is a rare congenital anomaly that occurs in 3-6% of patients with TOF (9). Absence of the pulmonary valve leads to pulmonary regurgitation and aneurysmal dilatation of the pulmonary arteries which results in compression of the tracheobronchial tree and thus significant respiratory compromise (10). The patients who present with respiratory symptoms within the first 3 months of life typically need surgery to correct abnormalities of TOF and to resolve the airway compression by revision of the enlarged pulmonary arteries (11). The need of preoperative ventilation for respiratory distress means severe airway compression by the aneurysm of the pulmonary arteries. The requirement of preoperative ventilation implies prolonged postoperative intubation and increased risk of mortality (12). Previously, only one case with Townes-Brocks syndrome which accompanied by APSV has been described (8). In this case, we detected APVS with TOF and dilated pulmonary arteries causing bilateral bronchial compression. Therefore, severe respiratory distress and need of mechanical ventilation were attributed to compression of the tracheobronchial tree by dilated pulmonary arteries. We attributed the need of early surgery and prolonged postoperative intubation to the requirement of preoperative mechanical ventilation due to severe respiratory distress. We considered that this heart defect might be associated with R276X mutation.

Genitourinary anomalies such as renal agenesis, renal hypoplasia, polycystic kidneys, dysplastic kidneys, posterior urethral valves, vesicoureteral reflux, and meatal stenosis may be observed in patients with TBS, as well as functional impairment of kidney with or without structural abnormalities (42% of individuals) (1, 13, 14). In the present case, we detected increased renal parenchymal echogenicity and mildly pelvicalyceal dilatation in both kidney. Transient renal functional impairment occurred within the first four days of life.

Brain neurons are particularly sensitive to SALL1 mutations (15). Therefore, central nervous system abnormalities such as intellectual disability (~10%), mental retardation, behavioral problems, cranial nerve palsy, hypoplasia of corpus callosum may be observed in the patients with TBS (1, 8, 16). Botzenhart et al (16) reported a child with TBS who suffered from seizures. Our patient had clonic seizure, although imaging of her central nervous system was normal.

Clinical ideas about the disease can be obtained with hand and wrist radiography such as pseudoepiphyses of the second metacarpal, fusion of triquetrum and hamate, absent triquetrum and navicular bones. In our patient, radiographs were taken for hand and wrist bone, but since no ossification had occurred, clinically supportive findings were not obtained from this area (1, 6, 15).

Features of TBS can overlap with other genetic syndromes. Goldenhar syndrome usually presents incomplete development of the nose, soft palate, lip, and mandible, but usually no upper limb or anal malformations and no overlapping toes. Okihiro syndrome has Duane anomaly and radial ray defects, but rarely hearing loss and renal anomalies. VACTERL association may present vertebral abnormalities and tracheo-esophageal fistula without ear anomalies or deafness, however severe vertebral defects and tracheo-esophageal fistula are not observed in TBS patients. Branchiootorenal syndrome is characterized by dysplastic ears, hearing loss or genitourinary malformations, but no thumb or anal anomalies (1, 7, 17).

In conclusion, TBS should be suspected in the presence of ear, anal and thumb malformations in a neonate. Further investigations should be performed for hearing loss, cardiac and genitourinary system anomalies, and finally genetic testing should be provided to confirm the diagnosis. If a patient with TBS and APVS needs preoperative ventilation within the first 3 months of life, this implies prolonged postoperative intubation and increased risk of mortality.

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Disclosure statement

The authors have no conflict of interests.

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Figure 1. Satyr's ear with overfolding of superior helices (a). Mildly protruding dysplastic right ear (b).

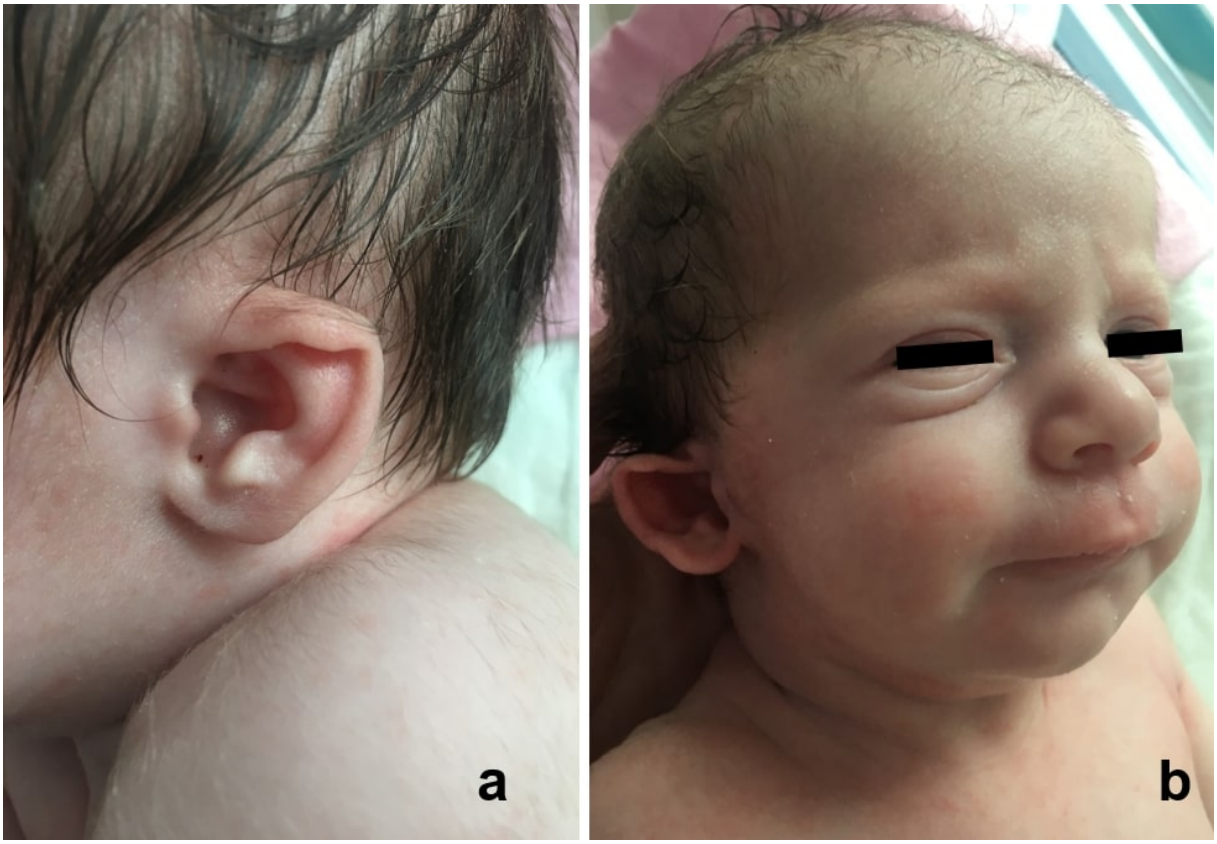

Figure 2. Triphalangeal thumb on the left hand (a) and preaxial polydactyly on the right hand (b). X-Ray examination of the hands showing triphalangeal thumb on the left (c) and preaxial polydactyly on the right (d).