CLINICAL QUIZ (p215) ANSWER

What is the diagnosis?

The clinical features of this child (preaxial polydactyly, toes syndactyly, chronic constipation and bilateral hearing impairment) were compatible with Townes-Brocks syndrome (OMIM # 107480). Townes-Brocks syndrome (TBS) is a rare disorder characterised by a classical triad of imperforate anus, dysplastic ears and thumb malformations.

Townes-Brocks syndrome was first described in 1972 By Townes and Brocks in a family with father and 5 of his 7 children who had imperforate anus, triphalangeal thumbs, and other anomalies of the hands and feet, including fusion of metatarsals, absent bones, and supernumerary thumbs.[1]

In view of the characteristic features of TBS, our patient had next generation sequencing performed and the analysis confirmed a reported nonsense pathogenic variant *SALL1* {NM_002968.2}:c.967C>T (p.Gln323*). Parental studies revealed the variant was de novo. The diagnosis of Townes-Brocks syndrome was substantiated.

Apart from those core features of TBS, renal impairment may occur with or without structural abnormalities in over 40% of TBS patients. Congenital heart disease can occur in 25% of patients. Over 50% of TBS patients would have foot malformations (e.g. flat foot and overlapping toes) and nearly 40% had genitourinary malformations. Intellectual disability occurs in approximately 10% of individuals. Rare features include iris coloboma, Duane anomaly, Arnold-Chiari malformation type 1, and growth retardation can also be found.[2]

The exact prevalence of TBS is not available.[2] The clinical manifestation is heterogeneous. Given the widely variable manifestations and clinical overlap with VACTERL association and other syndromes, many cases of TBS probably remain undiagnosed. The condition is rare with estimated prevalence of 1 per 250,000 without stringent diagnostic criteria use.[3]

How is the clinical diagnosis and molecular diagnosis established in Townes-Brocks syndrome?

The diagnosis of TBS is established in a patient with three major features. If only two major features are present, the presence of minor features and the absence of atypical features support the diagnosis. Identification of a heterozygous *SALL1* pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.[2]

Major features (% in TBS patients)	**Minor features (% in TBS patients)**
• Imperforate anus or anorectal malformation (84%)*	• Sensorineural and/or conductive hearing impairment (68%)**
• Dysplastic ears (87%)*	• Foot malformations (50%)**
• Typical thumb malformations without hypoplasia of the radius (89%)*	• Renal impairment with or without renal malformations (42%)**
	• Genitourinary malformations (36%)**
	• Congenital heart disease (12-25%)
Atypical features	
• Radius hypoplasia on clinical examination or radiographs	• Cleft lip/palate

*Percentages based on studies, a total of 61 persons with novel SALL1 pathogenic variants (not including the most common pathogenic variant, p.Arg276Ter)[4,5]

**Percentages based on studies[4-6]

Eighty-four percent TBS patients has imperforate anus or anal stenosis. They can also present as anteriorly situated anus, recto-vaginal or recto-urethral fistula and chronic constipation. Some patients may have gastroesophageal reflux symptoms. Eighty-seven percent of TBS patients would have dysplastic ears in the form of overfolded superior helices, preauricular skin tags/pits, or microtia/external ear underdevelopment or satyr ears. Thumb malformations, e.g. preaxial polydactyly, bifid/triphalangeal thumbs, and hypoplastic thumbs without hypoplasia of the radius were reported in 89% of TBS individuals. Sixty-seven percent of TBS individuals had the classic triad.

Congenital sensorineural and/or conductive hearing loss with variable severity can be found in 68% individuals. Clubfoot, overlapping toes (II and IV over III), syndactyly of toes, missing toes (III) were detected in around 50% of individuals. Forty-two percent of TBS individuals had renal agenesis, renal hypoplasia, polycystic kidneys or functional impairment with or without structural abnormalities. Congenital heart defects including atrial septal defect, ventricular septal defect, tetralogy of Fallot, truncus arteriosus, pulmonary valve atresia, and persistent ductus arteriosus were found in 50% TBS patients with the common *SALL1* p.Arg276Ter pathogenic variant or 12-25% TBS individuals with other *SALL1* variants.[7]

TBS results from mutations of the developmental gene spalt-like transcription factor 1 (*SALL1*) gene. SALL1 protein was found to be involved in ciliogenesis, cilia disassembly and elongation and Sonic Hedgehog (SHH) signaling. Thus TBS is considered as a ciliopathy.[8] No genotype-phenotype correlations have been made for the majority of pathogenic variants due to limited no of reported patients and most mutations are private. The most common pathogenic variant p.Arg276Ter is associated with more severe phenotype (higher percentage of patients with classical triad) and higher percentage of congenital heart defect than other pathogenic defects.

What are the conditions mimicking TBS?

The clinical presentation of TBS can overlap with Goldenhar syndrome (hemifacial microsomia), Okihiro syndrome, branchiootorenal syndrome (BOR) and VACTERL association.

Goldenhar syndrome patients have features of oculo-auriculo-vertebral spectrum phenotypes and do not have upper-limb or anal malformations. Okihiro syndrome (Duane-radial ray syndrome) is featured by Duane anomaly and radial ray defects, thumb aplasia and less commonly by hearing loss and renal position anomalies. Radial hypoplasia and thumb aplasia were not seen in TBS patients.

For BOR syndrome, individuals have thumb abnomalities together with ear malformations and renal malformation or impaired renal function. BOR syndrome is not associated with anorectal malformation.

VACTERL is characterised with **v**ertebral defects, **a**nal atresia, **c**ardiac defects, **t**racheo-esophageal fistula, **r**enal malformations, and **l**imb defects. It is an important differential diagnosis for patients with suspected TBS. Severe vertebral defects and tracheo-esophageal fistula were not reported in TBS patients. VACTERL association is a sporadic condition. For sibling or offspring recurrence risks of VACTERL association are estimated at approximately 1%.

Genetic counselling and management issues of TBS

TBS shows an autosomal dominant inheritance pattern, with the risk of inheriting TBS for children of affected parents being 50%. In sporadic cases, with non-affected parents, the recurrence risk in further pregnancies has been reported to be 1~5%. Sporadic cases are attributed to de novo mutations or germline mosaicism in parents.

Management of TBS prefers multi-disciplinary approaches involving paediatric orthopaedic surgeons, surgeons, geneticists, cardiologists, nephrologists, ENT surgeons and general paediatricians.

Immediate surgical intervention would be needed for imperforate anus. Hearing loss that is mild may worsen with age. Annual hearing evaluation is indicated. Early intervention should be provided for severe hearing loss. To improve the fine motor function, surgery for severe malformations of the hands would be indicated at early age.

Regular monitoring of renal function in individuals with and without renal anomalies should be considered. Hemodialysis and possibly kidney transplantation would be options for end-stage renal failure. Baseline echocardiogram is indicated to look for congenital heart defects.

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