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Endocrine Abnormalities in Townes–Brocks Syndrome

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Abstract

Townes–Brocks syndrome is a recognizable variable pattern of malformation caused by mutations to the *SALL1* gene located on chromosome 16q12.1. Only three known cases of Townes–Brocks syndrome with proven *SALL1* gene mutation and concurrent endocrine abnormalities have been previously documented to our knowledge [Kohlhase et al., 1999; Botzenhart et al., 2005; Choi et al., 2010]. We report on two unrelated patients with Townes–Brocks syndrome who share an identical *SALL1* mutation (c.3414_3415delAT), who also have endocrine abnormalities. Patient 1 appears to be the first known case of growth hormone deficiency, and Patient 2 extends the number of documented mutation cases with hypothyroidism to four. We suspect endocrine abnormalities, particularly treatable deficiencies, may be an underappreciated component to Townes–Brocks syndrome.

Keywords

Townes–Brocks syndrome; endocrine abnormalities; hypothyroidism; growth hormone deficiency; *SALL1*; preaxial polydactyly; triphalangeal thumbs

INTRODUCTION

Townes–Brocks syndrome (TBS) is a recognizable pattern of malformation with considerable phenotypic variability. TBS results from mutations in the *SALL1* gene, the official name sal-like 1 (*Drosophila*), which is a human homolog of SAL the developmental regulator of *Drosophila melanogaster*. In humans, the *SALL1* gene is located on 16q12.1 and encodes zinc finger domain proteins and alanine and glutamine heavy domains, all of which are associated with transcription factors. The prevalence of TBS in the general population has been estimated at 1 in 250,000 [Martinez-Frias et al., 1999], but is probably

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much higher due to common shared characteristics with VATER association and subtle variable phenotypes in many TBS patients [Miller et al., 2011]. The hallmark clinical features of TBS are the classic triad of anal, ear, and thumb anomalies [Kohlhase, 2007] which are inherited in an autosomal dominant manner [Townes and Brocks, 1972]. Other phenotypic variations include structural anomalies in the head and neck, cardiovascular, genitourinary, skeletal, neurologic, and/or endocrine systems. Definitive diagnosis is confirmed by molecular analysis for mutations in the *SALL1* gene.

Endocrine abnormalities have rarely been associated with TBS, with only three previously documented cases of hypothyroidism and a proven *SALL1* mutation [Kohlhase et al., 1999; Botzenhart et al., 2005; Choi et al., 2010]. We present two molecularly confirmed patients, clinically diagnosed with Townes–Brocks syndrome, who had endocrine abnormalities. Both unrelated patients harbored the c.3414_3415delAT mutation. This frameshift mutation is predicted to result in premature protein truncation.

CLINICAL REPORTS

Patient 1

A 3-year-old Caucasian male, the proband, was born at term to a 26-year-old G2P2 female. Pregnancy and delivery were notable only for maternal hypertension in the third trimester. Birth length was 51.4 cm (75th centile); birth weight was 3.58 kg (50th–75th centile). Evaluation by genetics occurred soon after birth due to a positive family history of TBS in a parent and sibling (Fig. 1, Family A, III-7, IV-1). Family A, IV-1 was also noted to have premature adrenarche at 4 months of age, which resolved spontaneously. Adrenal precursors and gonadotropins for Family A, IV-1, were within normal limits indicating no form of congenital adrenal hyperplasia or central precocious puberty. Clinical diagnosis of Patient 1 was TBS, which was molecularly confirmed as a *SALL1* mutation (c.3414_3415del AT).

Physical examination of the proband on initial presentation to genetics is summarized in Table I and was notable for microcephaly (Fig. 2) with subsequent measurements in normal range, mildly protruding, normally sized ears with over folding of superior helices (Fig. 3), mild micrognathia, a small anal tag, radial angulation of third fingers bilaterally, and lateral angulation of the halluces bilaterally. Thumbs appeared normal. Initial evaluation showed a normal renal ultrasound and two failed hearing tests. Follow-up brainstem auditory evoked responses (BAERs) were normal. Routine evaluation indicated bilateral hearing aids were required at 2 years of age. A follow-up renal ultrasound demonstrated mild hydronephrosis, which was followed by pediatric nephrology and later resolved.

Endocrinologic evaluation of growth deceleration commenced at 17 months of age. Final diagnosis was atypical growth hormone deficiency. Initially Patient 1 was diagnosed with milk and soy allergies that responded to formula changes. However, there was insufficient nutritional intake that required placement of a gastric feeding tube and caloric supplementation. Response to supplementation was minimal and work up for growth hormone deficiency revealed a low IGF1 of <17 (reference range: 25–142) and IGFBP3 of 516 ng/ml (reference range: 972–4123). While inadequate nutrition may have contributed to low IGF1 levels, a brain MRI confirmed a small pituitary (Fig. 4).

GH supplementation was initiated with an initial dose of 0.2 mg/kg/week (standard starting dose) at 17 months of age. Thyroid studies were normal before and after the start of growth hormone treatment. The ACTH stimulation test showed a normal cortisol peak. A bone age study was age appropriate.

Response of Patient 1 to the initial growth hormone replacement showed an increase in growth velocity to normal growth velocity parallel to growth curve, but without catch up growth (Figs. 5 and 6). To achieve catch up growth dose was increased to 0.29 mg/kg/week at 24 months, and again at 29 months to 0.4 mg/kg/week. While catch up growth has not yet been achieved, an increase in growth velocity is continuing to be observed.

Patient 2

Patient 2 (Fig. 7, Family B, III-1) is a 3-year-old Caucasian female born via induced vaginal delivery at 37 weeks gestation to an 18-year-old G1P1 female. Pregnancy was complicated by gestational diabetes and exposure to a combination of oxyco-done and acetaminophen, insulin, and caffeine. Birth length was 47.63 cm (10th–25th centile) and birth weight was 2.86 kg (50th–75th centile).

Newborn screening for hypothyroidism was abnormal and pediatric endocrinologic evaluation occurred on Day 32 of life. Clinical history of Patient 2 was remarkable for mild gastroesophageal reflux, mild hearing loss in the right ear, and moderate hearing loss in the left ear as tested by BAERs. Physical examination noted preaxial duplication of the distal phalanx of the thumb on the left hand (Fig. 8) and a palpable thyroid. TSH and T4 analyses showed a TSH level of 90.31 μ IU/ml (reference range of <20 μ IU/ml) and a free T4 that had decreased to 0.4 ng/dl (reference range of 0.58–1.64 ng/dl), confirming the diagnosis of primary hypothyroidism. A Technetium-99 scan on day 35 showed enlargement of the thyroid gland suggesting dysmorphogenesis. Treatment was begun with levothyroxine at an initial dose of 15 mcg/kg daily. Treatment for gastroesophageal reflux included changing to a soy formula.

Patient 2 was referred to the genetics from endocrinology because of familial thumb anomalies. The proband demonstrated mild Townes–Brock phenotype (Table I). Key physical examination findings consisted of over folding of the superior helix of left ear, duplication of left thumb (Fig. 8), and increased length and width of right thumb with a hypoplastic thenar eminence. BAERs were repeated and showed improvement to normal hearing in the right ear and mild hearing loss in the left ear. Renal ultrasounds were normal. Family history (Fig. 7) demonstrated a maternal autosomal dominant pattern of inheritance of thumb anomalies (Figs. 7 and 9), and paternal family history of hearing deficits unrelated to TBS family history. A limited physical exam was performed on Family B, II-2 (Fig. 7). Clinical evaluation suggestive of TBS was confirmed by molecular testing. A *SALL1* mutation in Patient 2 was present with a deletion of 2 nucleotides in exon 2 of the *SALL1* gene (c.3414_3415delAT; Fig. 1). Primary hypothyroidism was treated and followed by pediatric endocrinology. Constipation, which was initially thought to be related to hypothyroidism, did not resolve with levothyroxine treatment and currently requires anal stimulation for complete evacuation. This could be an expression of TBS as variable anal

malformations, including but not limited to strictures, may be contributing to the patient's constipation.

DISCUSSION

To date, only five instances of endocrine abnormalities in mutation positive TBS patients have now been reported (Table II). While both our patients have identical mutations, c. 3414_3415delAT of the *SALL1* gene, their endocrine abnormalities are different. Phenotype–genotype correlations are not supported when comparing other reports of c. 3414_3415delAT mutations (Table I).

Growth hormone deficiency has not previously been reported in Townes–Brocks syndrome associated with a proven *SALL1* mutation. It has been noted that *SALL1* is observed in various human adult and fetal tissues, which are involved with endocrine functions [Ma et al., 2002]. Most notably *SALL1* is expressed in the prenatal human pituitary–adrenal/gonadal axis. *SALL1* expression co-localizes with growth hormone in the anterior pituitary [Ma et al., 2002] providing evidence that supports the concept that in molecularly proven TBS patients with growth deceleration, growth hormone deficiency as well as hypothyroidism should be considered. Patient 1 did not achieve normalization of growth to date; however, improvement in growth velocity was observed.

Patient 2 (Table II) appears to be only the fourth confirmed case of hypothyroidism finding in a Townes–Brocks patient [Kohlhase et al., 1999; Botzenhart et al., 2005; Choi et al., 2010]. Other reports have identified hypothyroidism in patients with clinical features suggestive of TBS but without molecular verification [Yano et al., 1998; Goswami and Dubey, 2007; Park and Lee, 2008].

Table II provides a summary of molecularly proven gene mutations of *SALL1* in TBS patients with known endocrine abnormalities. The majority of these mutations are frameshift mutations thought to result in a truncated protein. Our clinical findings suggest that in all patients with molecularly proven Townes–Brocks syndrome, potential endocrine abnormalities should be considered, particularly in those cases with deletions resulting in frame-shift mutations. These cases suggest that endocrine abnormalities are an underappreciated component of TBS.

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FIG. 1. Pedigree of Patient 1 (Family A) with a description of clinical symptoms of Townes–Brocks syndrome in family members with known *SALL1* gene mutation c.3414_3415delAT or unknown genotype.

FIG. 2.
Patient 1 showing facial phenotype with mild micrognathia and mildly protruding ears.

FIG. 3.
Patient 1 showing over folding of superior helices.

FIG. 4.
Sagittal T1 magnetic resonance imaging of Patient 1's cranium demonstrating a small pituitary.

FIG. 5.

Growth of Patient 1 plotted on the CDC growth chart. The solid arrow at 17 months indicated the initiation of growth hormone therapy with standard starting dose of 0.2 mg/kg/week. At 24 months, his dose of growth hormone replacement was increased to 0.29 mg/kg/week indicated by the long-dashed arrow at 24 months. At 29 months, his dose of growth hormone replacement was again increased to 0.40 mg/kg/week indicated by the short-dashed arrow.

FIG. 6.

Growth of Patient 1 head circumference in centimeters plotted on the CDC growth curves. The solid arrow at 17 months indicates the initiation of growth hormone therapy with standard starting dose of 0.2 mg/kg/week. At 24 months, his dose of growth hormone replacement was increased to 0.29 mg/kg/week indicated by the long-dashed arrow at 24 months. At 29 months, his dose of growth hormone replacement was again increased to 0.40 mg/kg/week indicated by the short-dashed arrow.

	Phenotype	Genotype
I. 1	Thumb abnormalities	Unknown
II. 2	Thumb abnormalities	c.3414_3415 delAT
II. 3	Thumb abnormalities	c.3414_3415 delAT
III. 1	Thumb abnormalities	c.3414_3415 delAT
III. 2	Spontaneous abortion at 20 weeks	c.3414_3415 delAT
III. 3	No known abnormalities	No known mutation

FIG. 7.
Pedigree of Patient 2 (Family B) with descriptions of clinical features of Townes–Brocks syndrome in family members with known *SALL1* gene mutation c.3414_3415delAT or unknown genotype.

FIG. 8.
Patient 2 showing left thumb duplication.

FIG. 9.
Patient 2 mother showing widening of the left thumb and duplication of the right thumb and bilateral distal ulnar deviation of both thumbs.

TABLE 1

Genotype-Phenotype Comparison of Known SALL1 Gene Mutation c.3414_3415delAT

Patient	Hearing	Ears	Renal	Hands	Feet	Anus	Gastro-esophageal	OFC	Endocrine	Incidental finding
Family A, IV-2	Requires hearing aids	Over folding of superior	Hydro-nephrosis (resolved)	Deviation of digit 3 bilaterally at distal phalanges	Halluces wide and short with deviation laterally	1. Anal tag	GER	Microcephalic	1. Growth Hormone deficiency	None
Family A, IV-1	No issues	1. Size: <2 SD bilaterally	Vesiculoureteral reflux	1. Proximally placed thumb	Unremarkable as seen by geneticist	2. Raphe present Anal atresia with rectovaginal fistula	No issues	1 year: <15th percentile	2. Small pituitary 3. Normal thyroid Precocious adrenarche at 4 months, which resolved spontaneously and with unknown etiology	1. PFO
Family B, III-1	Left hearing loss	Left over folding of superior helix	No issues	1. Left thumb duplication	Unremarkable as seen by geneticist	Unremarkable as seen by geneticist	No issues	Narma cephatic (OFC ranged between 10% and 50% centile)	Primary hypothyroidism	None
20.1 [Botzenhart et al., 2007]	No issues commented	Malformed ears	No issues commented	1. Bilateral preaxial Polydactyly 2. Widening of right thumb	No issues commented	Imperforate Anus	No issues commented	No issues commented	No issues commented	No issues commented
20.2 [Botzenhart et al., 2007]	No issues commented	Bilateral over folder helices	Kidney length asymmetry	1. Duplicated right thumb 2. Triphalangeal left thumb	No issues commented	1. Imperforate anus 2. Sacral dimple	No issues commented	No issues commented	No issues commented	Asymmetric nipple displacement
20.3 [Botzenhart et al., 2007]	Hearing difficulties	No issues commented	No issues commented	Described as extra bones in both thumbs	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented

Patient	Hearing	Ears	Renal	Hands	Feet	Anus	Gastro-esophageal	OFC	Endocrine	Incidental finding
GDA 18 [Weber et al., 2006]	No issues commented	No issues commented	Bilateral hypoplasia	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented
0x2948 [Furniss et al., 2007]	No issues commented	No issues commented	No issues commented	1. Preaxial Polydactyly 2. Triphlangeal thumb	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented	No issues commented

Family A, IV-2 refers to Patient 1. Family A, IV-1 refers to sister of Patient 1. Family B, III-1 refers to Patient 2. The mother of patient 2 was not included in this chart as there is limited history and physical information. Physical examinations were performed by Carolyn Bay, MD.

TABLE II***SALL1* Gene Mutations With Endocrine Abnormalities**

Patient	Gene mutation	Endocrine abnormality
Patient 1	c.3414_3415delAT	Growth hormone deficiency
Patient 2	c.3414_3415delAT	Congenital hypothyroidism
Patient 4-1 [Kohlhase et al., 1999]	826C→T	Hypothyroidism
Family J [Botzenhart et al., 2005]	c.1374delT	Congenital hypothyroidism
Patient X [Choi et al., 2010]	c.1470delG	Congenital hypothyroidism