Townes-Brocks Syndrome Associated with Hypothyroidism in a Korean Newborn : A Case Report

Shin Young Park · Woo Ryoung Lee

Department of Pediatrics, School of Medicine, Soonchunhyang University, Seoul, Korea

Townes-Brocks syndrome (TBS) is an autosomal dominant disorder with multiple malformations which include dysplastic ears, hearing loss, preaxial polydactyly and/or triphalangeal thumbs, imperforate anus, renal anomalies, congenital heart defects, and mental retardation. However, hypothyroidism is not a common feature of TBS. There have been only three reported cases of TBS associated with hypothyroidism. We report the first case of TBS associated with hypothyroidism in Korea.

Key Words: Townes-Brocks syndrome, Hypothyroidism, Newborn

Introduction

Townes-Brocks syndrome (TBS) is a rare autosomal dominant disorder caused by mutations in *SALL1*, a gene mapped to 16q12.1[1]. Major anomalies include external ear anomalies (microtia, "satyr" or "lop" ears, and preauricular tags or pits), hearing loss, preaxial polydactyly and/or triphalangeal thumbs, anal atresia, and renal malformations[1, 2]. Cardiac anomalies, mental retardation, and hypothyroidism are rare in this syndrome[1]. Since Townes and Brocks first described this syndrome in 1972[1], a further 66 cases have been reported. There have been only three reported cases of TBS associated with hypothyroidism prior to this report[3-5]. We report the first case of TBS associated with hypothyroidism in Korea.

접 수: 2008년 8월 11일
수정본접수: 2008년 9월 20일
게재승인일: 2008년 9월 24일
게 재 일: 2008년 12월 31일
Corresponding author: Woo Ryoung Lee M.D.
Department of Pediatrics, Soonchunhyang University Hospital, Daesaguangil 22, Yongsan-gu, Seoul 140-743, Korea
Tel: +82-2-709-9346, Fax: +82-2-794-5471
E-mail: neolee@hosp.sch.ac.kr

Case Report

The patient was a male preterm baby. He was born by caesarian section at the 34th week of gestation with a birth weight of 2,330 g, a length of 47.5 cm, and a head circumference of 30.5 cm. He was the second child; his older brother was normal. He had an imperforate anus, right preaxial polydactyly, lop ears, and a right preauricular skin tag at birth (Fig. 1-3). His mother also had a congenital imperforate anus corrected by surgery and one-sided sensorineural hearing loss. No other family members were affected. Chest X-ray showed signs of respiratory distress syndrome at birth. He received surfactant therapy and his respiratory symptoms improved. The initial laboratory findings were not remarkable. The blood urea nitrogen (11 mg/dL) and serum creatinine (1.3 mg/dL) were within the normal range at first but soon became elevated to 65 mg/dL and 3.1 mg/dL, respectively, on the 6th day of life. Abdominal ultrasonography showed cortical cysts and increased cortical echogenecity of both kidneys. A neonatal thyroid function test revealed hypothyroidism (TSH 58.4 μU/mL, free T4 0.91 ng/dL, and T3 192 pg/mL). After 18 days of levo-

Fig. 1. Right preaxial polydactyly.

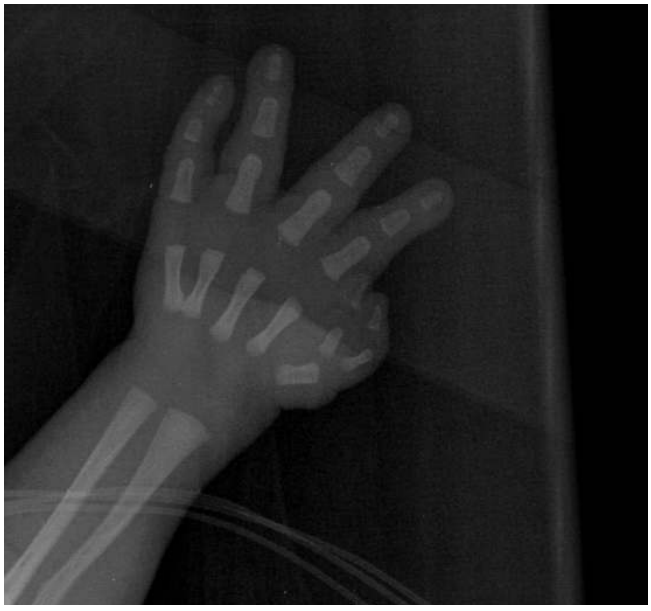

Fig. 2. Double proximal and distal phalanges on the right hand.

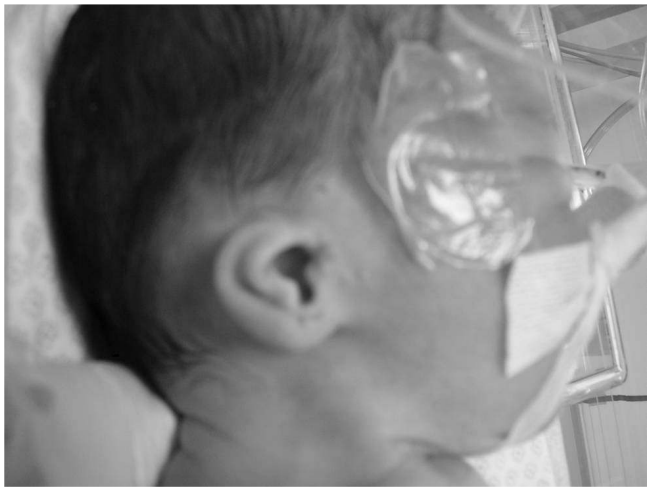

Fig. 3. Right lateral view of lop ear and preauricular skin tag.

thyroxine treatment, thyroid function was improved and TSH, free T4, and T3 were changed to 2.07 mIU/L, 1.06 ng/dL, and 59.4 pg/mL, respectively. A thyroid ultrasonography scan showed no abnormalities. The response evoked from the auditory brainstem was sluggish, but computed tomography of temporal bones showed no structural abnormalities.

After all the abnormal laboratory findings were normalized by appropriate treatments, the patient was discharged on the 43rd day of life. However, he was readmitted again on the 54th day of life with continuous vomiting and constipation for 3 days. He expired because of acute renal failure caused by severe dehydration and electrolyte imbalance.

Discussion

Townes and Brocks first described Townes-Brocks syndrome in 1972[2]. They reported a family in which the father and five of his seven children had an imperforate anus, triphalangeal thumbs, and other limb abnormalities including fusion of metatarsals, absent bones, and supernumerary thumbs[2]. Other features included mild sensorineuronal deafness and lop ears[2].

Since then, 66 additional cases have been described[1]. TBS is estimated to occur in about one out of 250,000 live borns[5] but may be misdiagnosed because its defects overlap with other genetic diseases such as VACTERL association[6], Pendred syndrome, oculoauriculovertebral spectrum, Baller-Gerold syndrome, and Cat eye syndrome[1].

Townes-Brocks syndrome is a rare disease of autosomal dominant inheritance but approximately 50% of TBS cases are sporadic and due to *de novo* mutations in the *SALL1* gene.

Mutations in the candidate gene, *SALL1*, have been found in one family and in an isolated case with typical features of this syndrome[7]. Thirty-five mutations have been identified in the *SALL1* gene. Most mutations were found in the 5-prime to or within the region encoding the

first double zinc finger[4]. The gene for Townes-Brocks syndrome was mapped to 16q12.1 by identifying subjects with TBS and cytogenetic abnormalities.

The diagnostic criteria suggested for TBS include two or more of the following: anorectal malformations (imperforate anus, anteriorly placed anus, and anal stenosis), hand malformations (preaxial polydactyly, triphalangeal thumbs, and bifid thumbs), external ear malformations (microtia, "satyr" or "lop" ears, preauricular tags and fits) with sensorineuronal hearing loss, and a relative with the syndrome[1, 8]. Renal-ear-anal-radial (REAR) syndrome is also a term that has been used to describe this condition[9].

Besides these main characteristics, a high incidence of genitourinary abnormalities is found in TBS. These include unilateral or bilateral hypoplastic or dysplastic kidneys, renal agenesis, multicystic kidneys, posterior urethral valves, vesicoureteral reflux, and meatal stenosis[10]. This highlights the need for renal evaluation and monitoring of renal function in TBS patients. Other intermittently observed features include mental retardation, eye abnormalities, and spine abnormalities[1].

In this case, we were not able to perform genetic evaluation due to parental refusal. However, the clinical signs and laboratory findings were consistent with TBS. In addition to the major reported features, our patient also had hypothyroidism.

To the best of our knowledge, there have been only three case reports of Townes-Brocks syndrome associated with hypothyroidism[3-5]. The first case was a Japanese boy, reported in 1998 by Yano et al[3]. The patient was described to have typical TBS associated with Pendred syndrome. Pendred syndrome is an autosomal recessive disorder which is characterized by sensorineural hearing loss and a defect in the organification of thyroid hormones. The second case was a German male, reported by Botzenhart et al. in 2005[4]. The patient had elevated TSH levels in the cord blood in the neonatal screening test and received thyroxine replacement therapy. The third case was an Indian girl, reported by Goswami and Dubey in 2007[5].

In this study, we report the first Korean case of Townes-Brocks syndrome associated with hypothyroidism.

국문초록

Townes-Brocks 증후군은 이형성 귀, 청력 상실, preaxial polydactyly, triphalangeal thumbs, 쇄항, 신기형, 선천성 심질환, 정신 지체 등을 동반하는 다기형의 상염색체 우성 유전질환이다. 그러나 갑상선 기능저하증은 Townes-Brocks 증후군의 흔한 특징은 아니다. 현재까지 갑상선 기능저하증과 동반된 Townes-Brocks 증후군은 3례가 보고된 바 있다. 저자들은 한국에서 최초로 갑상선 기능저하증과 동반된 Townes-Brocks 증후군 1례를 보고한다.

References

1) Powell CM, Michaelis RC. Townes-Brocks syndrome. J Med Genet 1999;36:89-93.
2) Townes PL, Brocks ER. Hereditary syndrome of imperforate anus with hand, foot and ear anomalies. J Pediatr 1972;81:321-6.
3) Yano S, Watanabe Y, Yoshino M. Townes-Brocks and Pendred syndrome in the same patient. Am J Med Genet 1998;77:330-1.
4) Botzenhart EM, Green A, Ilyina H, König R, Lowry RB, Lo IF, et al. *SALL1* mutation analysis in Townes-Brocks syndrome: twelve novel mutations and expansion of the phenotype. Hum Mutat 2005;26:282.
5) Goswami V, Dubey NK. Townes-Brocks syndrome with hypothyroidism. Indian Pediatr 2007;44:140-2.
6) Hong YH, Lee DH. The developmental biology of birth defect. J Genet Med 2008;5:1-5.
7) Kohlhase J, Wischermann A, Reichenbach H, Froster U, Engel W. Mutations in the *SALL1* putative transcription factor gene cause Townes-Brocks syndrome. Nat Genet 1998;18:81-3.
8) Aylsworth AS. Anus-hand-ear syndrome. Blackwell Scientific Publications, 1990:155.
9) Kurnit DM, Steele MW, Pinsky L, Dibbins A. Autosomal dominant transmission of a syndrome of anal, ear, renal and radial congenital malformation. J Pediatr 1978;93:270-3.
10) Newman WG, Brunet MD, Donnai D. Townes-Brocks syndrome presenting as end stage renal failure. Clin Dysmorphol 1997;6:57-60.